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Cancer Sciences

The evaluation of "Lower Gastrointestinal e-Referral Protocol" at the Primary care-Secondary care interface. A prospective study

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Abstract

The rationale for this study was born out of the need to streamline referral mechanisms for suspected colorectal cancer referrals from primary care, and also to process patients with lower gastrointestinal symptoms and suspected iron deficiency anaemia adequately. There is limited guidance on how to decide which patients need investigations and no clear guidance in primary care on where patients with various colorectal symptoms should be seen in secondary care. We hypothesized that a validated electronic referral protocol (e-RP) addressing the full spectrum of lower gastrointestinal symptoms and suspected or proven iron deficiency anaemia would help General Practitioners in making correct referral decisions.

This prospective, parallel, non-randomised trial looking at the benefits of a dedicated Lower Gastrointestinal e-Referral Protocol was carried out in one secondary care hospital and surrounding general practices in the Bournemouth and South & East Dorset Primary Care Trusts. My aim was to assess the yield of CRC, whilst filtering less serious pathology, from the TWW and urgent referral system. I measured the time periods from referral by GP through first appointment/investigation to definitive diagnosis in groups of patients who were referred using the e-RP or through traditional referral methods.

The use of e-RP was associated with a statistically significant increase in yield of CRC, difference in time to definitive diagnosis for colorectal cancer and a sensitivity of 100%, compared with 75% for non-use of e-RP. There were several other changes which support the use of e-RP but which did not reach statistical significance, probably due to Type II error.

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A Declaration of Authorship

I, Solomon Kuruvilla Parappallichirayil John Declare that the thesis entitled **The evaluation of "Lower Gastrointestinal e-Referral Protocol" at the Primary care – Secondary care interface. A prospective study** and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;

- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

- where I have consulted the published work of others, this is always clearly attributed;

- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

- I have acknowledged all main sources of help;

- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

- parts of this work have been published as:

Original Papers

1.Symptoms and signs in patients with colorectal cancer, A review; **John SKP**, George S, Primrose JN, Fozard JBJ. **Colorectal Disease; 2011**; Jan;13(1):17-25

2.Validation of the Lower Gastrointestinal Electronic Referral Protocol; **John SKP**, George S, Howell RD, Primrose JN, Fozard JBJ. **British Journal of Surgery**; 2008; 95:506-514

3. Inter General Practice Variability in Use of Referral Guidelines for Colorectal Cancer; **John SKP,** Jones OM, Horseman N, Thomas P, Howell RD, Fozard JBJ; **Colorectal Disease,** 2007; 9: 731-735

Abstracts

1."More CRC, More A&B, Results from a Prospective Trial of Decision Support in Primary Care". **BJS 2008; 95 (S3), p 75-76**

2.Decision support pathway in "choose and book" for colorectal referrals-a way forward. **BJS 2007; 94(S2): 38**

3.Targeted education and option to use a Decision Support Protocol (DSP) within primary care-Possible solution to earlier diagnosis of colorectal cancer. **BJS 2007; 94(S2): 38**

4.Inter general practice variability in referral of patients suspected of having colorectal cancer- a Hugh education gap. **BJS 2007; 94(S2): 38**

5.'Lower GI electronic referral protocol'. Analysis of 300 referral episodes. **BJS 2006 Supplement, Vol 93, 05/2006.**

6.Targeted education and option to use a Decision Support Protocol (DSP) within primary care-Possible solution to earlier diagnosis of colorectal cancer. **Colorectal Disease, Supplement 2, 2007; Vol 9.**

7.Inter general practice variability in referral of patients suspected of having colorectal cancer- a Hugh education gap**. Colorectal Disease, Supplement 2, 2007; Vol 9.**

Signed: ……  …….

Date:……21/03/2010……

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Definitions & Abbreviations Used

CRC - Colorectal Cancer

PCT- Primary Care Trust

e-RP- “Lower Gastrointestinal Electronic Referral Protocol”

S E Dorset – South and East Dorset

DoH - Department of Health

ONS – Office of National Statistics

SWCIS – South West Cancer Intelligence Service

TWW –Two-Week Wait Rule

GPs – General Practitioners

UK – United Kingdom

NHS – National Health Service

PPV – Positive Predictive Value; NPV- Negative Predictive Value

CI – Confidence Interval

RR – Relative Risk

CIBH – Change In Bowel Habit; RB – Rectal Bleeding; IDA –Iron Deficiency Anaemia

IBD – Inflammatory Bowel Disease

CT – Computerised Tomography Scan

MRI – Magnetic Resonance Imaging

PET – Positron Emission Tomography

FoB – Faecal Occult Blood

ACPGBI – Association of Colo-Proctology of Great Britain & Ireland

UA/LA – Unitary Authority / Local Authority

LREC- Local Regional Ethics Committee

1.Introduction

The Benign Diseases

Colorectal pathologies span the whole spectrum, from purely benign causes like haemorrhoids and irritable bowel syndrome to neoplastic processes of varied natures. It has been well demonstrated, both in the general population and in primary care, that there exists a significant overlap in the various symptoms and signs for all these conditions. Any mechanism implemented to improve referral pathways for colorectal cancer would, therefore, have to take into consideration more serious benign pathology, such as inflammatory bowel disease, while avoiding delays for both groups of patients.

The Intermediate Group

This group of patients sandwiched between the purely benign conditions like haemorrhoids, fissures in ano, etc, and colorectal cancers, mainly comprises polyps and familial neoplastic syndromes. The polyps could vary as to histological type (eg. adenomatous, metaplastic, etc), degree of dysplasia, size of polyps and presence or absence of villous architecture. Hereditary conditions with a high risk of CRC in the future, i.e. FAP, HNPCC, etc, also fall into this category. This thesis deals predominantly with colorectal cancer, though it will briefly cover the various pathologies mentioned in this group.

Colorectal Cancers

Cancer is responsible for over a quarter of deaths in the UK. This figure may be reduced by improving treatments for the disease, or by treating the disease earlier in its course. For several cancers the prognosis is improved by early diagnosis: this is the rationale for screening programmes such as mammography or cervical cytology. However, of the four commonest cancers in the UK – lung, breast, colorectal and prostate – only breast cancer had an ongoing screening programme until colorectal cancer screening programme was phased in from April 2006.

At present, colorectal, lung and prostate cancers are generally diagnosed after they have caused symptoms. Patients presenting with these symptoms discuss them with their General Practitioners (GPs), who will perform an examination and organise simple tests. If there is a high suspicion of cancer, then the General Practitioner will refer the patient to a specialist for a particular investigation to confirm – or refute – the diagnosis. While this sounds simple and straightforward, the actual situation is much more complex, primarily because of the high prevalence of colorectal symptoms presented to GPs. To separate out the patients with a high-risk of colorectal cancer and refer them appropriately requires both knowledge and clinical acumen. Sending these possible colorectal cancer patients

through appropriate clinical pathways to secondary care is of the utmost importance to prevent delay in diagnosis and management.

This thesis tries to assess the benefit of validated decision support software (Lower Gastrointestinal Electronic Referral Protocol {e-RP}) in assisting GPs making appropriate decision on referral of these patients to secondary care. The e-RP software aims to assist GPs in appropriately directing referrals to secondary care while improving the yield of colorectal cancer (CRC) from primary care through the Department of Health (DoH)-established two-week-wait clinics (TWW) for suspected cancer.

1.1 Comparison Of Colorectal Cancer With Other Main Cancers And Their Relevance To This Thesis

Epidemiology, Survival and Global Size of the Problem

Globally, colorectal cancer is the third most common cancer and the fourth most frequent cause of cancer deaths worldwide. The World Health Organisation (WHO) estimates that 945 000 new cases occur yearly, with 492 000 deaths[1 2].

Colorectal cancer, once a disease of the west, is now seen throughout the world regardless of a country's stage of development, posing both a public health and a political problem. Worldwide, there were 783,000 new cases diagnosed in 1990, accounting for 9.4% of all cancers in men and 10.1% in women[3].

The incidence of colorectal cancer is not the same throughout the world; however, in this respect it is still predominantly a disease of developed countries. The incidence in high-risk, western countries such as North America, Australia, New Zealand, and Northern and Western Europe, is ten times higher than that of the low-risk, developing countries for colon cancer, and seven times higher for rectal cancer (an incidence of 3.4 cases per 100,000 in Nigeria compared to an incidence of 35.8 cases per 100,000 in certain areas of the United States of America)[2;4]. This relationship is not static, however, with both high-risk and low-risk countries reporting changes in incidence for better and worse[2].

Colorectal cancer incidence also varies markedly with age, from 3.7/100,00 in females and 4.2/100,000 in males under 45, to more than 333/100,000 in women and 500/100,000 in men over 85[5;6]. This lower age cut-off has been incorporated in the design of the e-RP. Recent literature quotes a lifetime incidence of 5% in developed countries, though both incidence and mortality are now decreasing[7;8]. The worldwide variability of outcome is proportional to access to specialists and the availability of modern drug therapy; the overall 5-year survival rate in the USA exceeds 60%, but is lower than 40% in less-

developed countries[1].

Prevalence of Cancer in the United Kingdom

Recently, prevalence estimates of cancers in the UK have been successfully calculated using data from over half the English population, the complete Scottish population and extrapolating to the Northern Ireland and Welsh populations the prevalence rates of Scotland and England using incidence and mortality data from the EUROPREVAL study[9].

Approximately 1.5% of the male population and 2.5% of the female population were living with cancer in 1992. Prevalence was higher in Scotland than in England, in both sexes, for cancers of the colon and lung and for melanoma of the skin. Prevalence was higher in England for cancers of the rectum and prostate in males and cancers of the breast and uterus in females. Cancer prevalence increased steeply with age, reaching values of 7.3% and 7.8% in males and females, respectively, in the ≥65 years age group. In this group, the most prevalent cancers were those of the prostate, lung, colon and rectum in males, and of the breast, colon and uterus in females. The pattern was similar among the middle-aged population (45–64 years), although the absolute prevalence estimates were substantially lower, especially for prostate cancer in males.

The Disease Burden in the United Kingdom

For both sexes, three sites account for approximately 50% of cancer incidence and mortality; in males these are lung, prostate, and colorectal cancer, in females breast, colorectal, and lung cancer[10;11]. The four most common cancers – breast, lung, colorectal and prostate – accounted for just over half of the 233,600 new cases of cancer (excluding non-melanoma skin cancer) registered in England in 2004 (Figure 1).

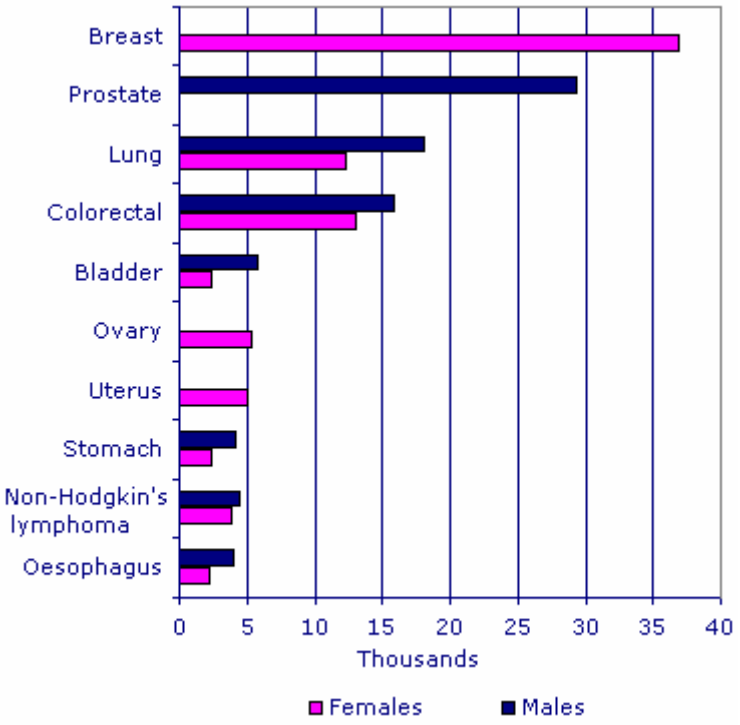


Figure 1 Incidence of common cancers in England in 2004[12]. *(Courtesy of ONS)*

The incidence of cancer is not evenly distributed between the sexes and age groups (Figure 2 and 3). Rates begin to increase during the 4th decade of life, though the initial rate of increase is greater in women – in the 40-44 years group the rate for women is double that for men. From then on, the rate increases more sharply in men – by 60-64 years the rates are roughly equal, by 65-68 years the rate for men is approx 45% greater than that for women, and by 80-84 years the rate is almost double that of women. The peak cancer incidence in both sexes is during the 8th decade of life (70-79)[5]. It is not unreasonable to estimate that an incidence of approximately 1 in 3 individuals will be diagnosed with some form of malignancy (excluding non-melanoma skin lesions) during their lifetime, though it will not necessarily be the cause of death.

Approximately one half of all living male cancer patients had survived for >5 years and one-third had survived for >10 years. For females, these proportions were higher at 60% and 40%[9].

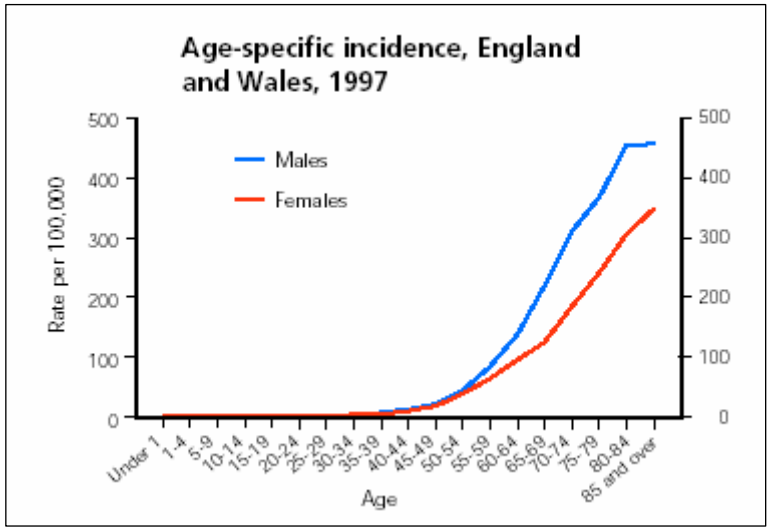


Figure 2 Age specific incidence of colorectal cancer in England and Wales[5], (reproduced from Quinn et al 2001)

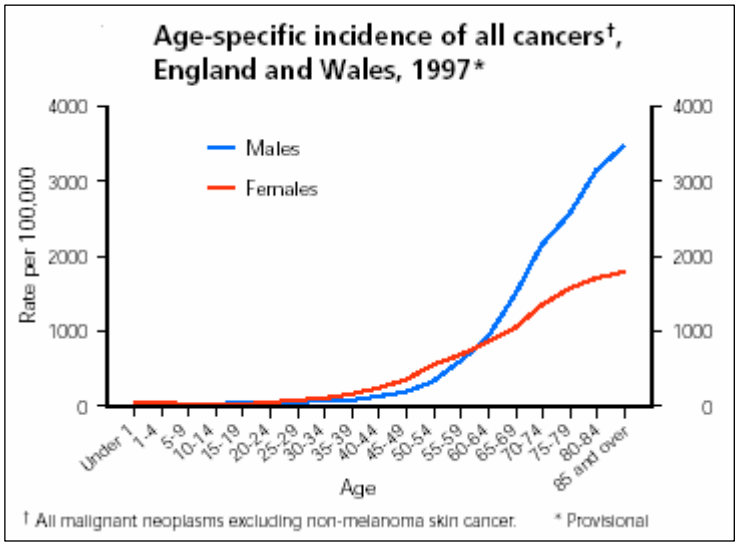


Figure 3 Incidence of all cancers: frequency distribution by age in England and Wales[5] (reproduced from Quinn et al 2001).

		1991-99 incidence No. (% of total)	1991-2000 deaths No. (% of total)	Lifetime Risk	Survival	
					1yr	5yr
Lung Cancer	♂	27,000 (20.2%)	24,300 (28.6%)	1/13	20%	5%
	♀	15,000 (11%)	13,400 (17.1%)	1/23		
Colorectal Cancer	♂	17,600 (13.1%)	9,500 (11.1%)	1/18	70%	40%
	♀	16,300 (11.9%)	9,100 (11.5%)	1/20		
Breast Cancer		38,900 (28.5%)	14,600 (18.6%)	1/9	90%	75%
Prostate Cancer		22,500 (16.8%)	10,000 (11.8%)	1/14	80%	50%

Table 1 Summary and comparison of the four major forms of cancer in the UK and Ireland [10;12;13].

Incidence and Mortality of Colorectal cancer

Total colorectal cancer incidence in 1997 was 28,900, 13% of the total reported (14,600 deaths). This compares with 33,300 cases of lung cancer in the same year (29,400 deaths), 33,100 cases of breast cancer (11,500 deaths) and 18,300 cases of prostatic cancer (8,500 deaths).

Trends in Incidence, Mortality and Survival

The incidence of colorectal cancer has seen little change over the last 50 years, though there has been a small but gradual increase among males since 1971. This has been accompanied by a small but steady fall in mortality since 1950, largely due to improvements in treatment. The five-year survival from colon cancer increased in both sexes to around 50% (2.5% higher in both sexes) for patients diagnosed in 1998-2001, compared with results for patients diagnosed during 1996-99. Differences in survival between the four main cancers are summarized in Table 1.

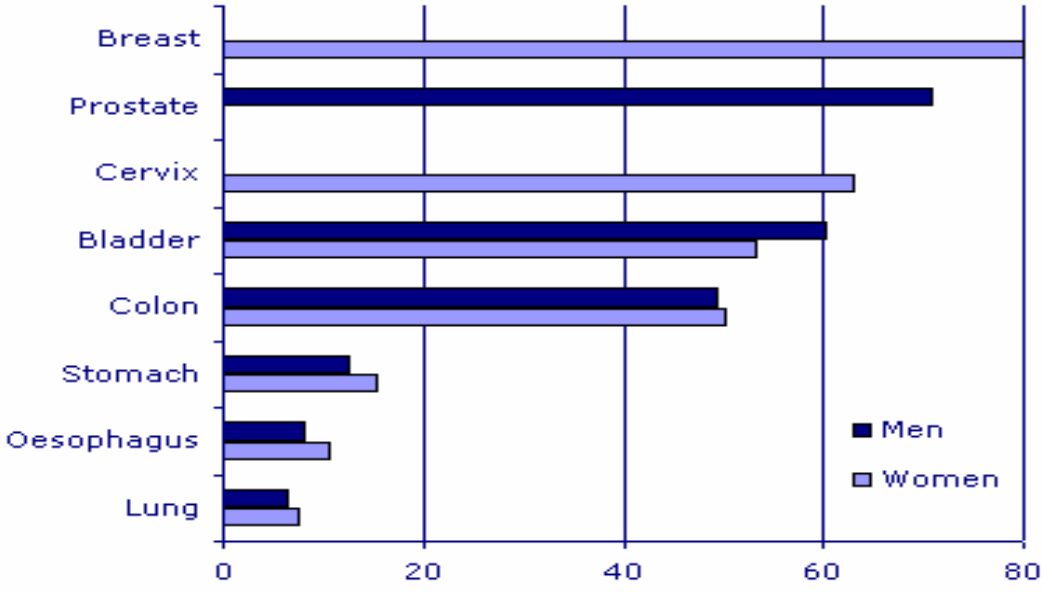


Figure 4 Five -year relative survival rates for selected cancers: for adults diagnosed during 1998-2001 in England (Courtesy ONS).

Effects of Age, Sex and Social Deprivation on Survival

Although many factors influence cancer incidence and mortality, age, sex and social deprivation are the most consistent demographic features exerting an effect. The majority of cancers demonstrate poorer survival with increasing age at diagnosis, and this is also the case with lung cancer. Lung cancer is increasingly a disease of the elderly, as the smoking population ages and changing smoking trends take effect. It was estimated that by 2005 over 40% of lung cancer patients would be 75 years or over at presentation[6;13;14].

By comparison, age has less effect on colorectal cancer survival than on the other four major cancer types, with less than 10% variation in survival over the 40-79 age range[13]. However, it is the only one of the four major malignancies discussed here in which gender can be truly seen to have an effect: breast and prostate cancer are, in the main, gender specific while lung cancer is influenced so strongly by greater than that of females across all age groups during the 1950-1999 period[5]. smoking habits. The age specific incidence of colorectal cancer for males was consistently

Colorectal cancer demonstrates socio-economic trends for males and females in both sub-sites, though the most marked and consistently identified trend is seen among men with rectal cancer. A positive gradient is seen in both incidence and mortality – incidence is 25% higher and mortality 50% higher in social class V compared to social class I[5;11].

1.2 Aetiology Of Colorectal Cancer

Significant advances have been made in the study of colorectal cancer over the last decade. A more thorough understanding of the molecular basis of this disease, coupled with awareness of important interactions, both genetic and environmental, have contributed to methods aimed at primary prevention, screening and early detection in susceptible families.

Multiple factors are responsible for transformation of a normal mucosa to a premalignant adenomatous polyp to a frank colorectal cancer over the course of many years (adenoma-carcinoma sequence)[15]. However, recent literature has mentioned the role of colorectal cancers arising de novo, rather than in a sequential fashion as an adenoma-carcinoma sequence[16], though this has not been fully accepted. Another model "the Serrated Neoplasia pathway" is described in case of serrated adenomas.This term was first coined in 1990 by Longacre and Fenoglio-Preiser to describe a discrete neoplastic lesion with a distinctive serrated architecture that contained areas of epithelial dysplasia. The serrated neoplasia pathway suggests that dysplasia can arise within hyperplastic colonic polyps, resulting in the formation of a serrated adenoma and potentially the development of colorectal carcinoma. The polyps of this pathway differ morphologically and genetically from polyps associated with the traditional adenoma–carcinoma sequence. They are characterized microscopically by the presence of crypts with prominent serrations and are characterized by certain genetic changes, including the presence of microsatellite instability in many cases[17;18]. This has shed more light on hyperplastic polyps, which have been almost always considered benign with no propensity for malignant transformation.

Most colorectal cancers are sporadic. About 20% of all patients with this cancer have some component of familial risk without fulfilling the strict criteria for hereditary colorectal cancer [19]. Hereditary colorectal cancers account for 5 to 10% of total colorectal cancers and, in 1 to 2% there is history of inflammatory bowel disease. Hence it is of paramount importance to enquire about the family history of patients suspected of having colorectal cancer. Guidelines from the British Society of Gastroenterology and others, such as the Revised Bethesda guidelines, are useful in this context.

Diet

Obesity and increased daily total calorie intake have been found to be independent risk factors for colorectal cancer. Increased body mass index (BMI) may result in twice the risk of colon cancer compared to rectal cancer, especially in men[20;21].

Dietary fibre has been hypothesised to reduce the risk of colorectal cancer, possibly by dilution of faecal carcinogens and procarcinogens, reduction of transit time of faeces

through the bowel, production of short chain fatty acids, which promote anticarcinogenic action, and binding of carcinogenic bile acids[22;23]. However, a recent pooled analysis of 13 prospective cohort studies showed that an increased intake of dietary fibres did not exhibit a linear inverse relationship with colorectal cancer. Though high fibre may not have a major effect on risk of CRC, a diet high in dietary fibre from whole plant foods would still be advisable due to a definite reduction in risks noted with conditions such as heart disease and diabetes.

Red meat, along with fried, barbecued and processed meats have been definitely associated with increased risk of CRC, especially rectal cancer with a odds ratio of 6[2]. Fatty components of red meat may be tumour promoters as they are metabolised by luminal bacteria to carcinogens, which would cause abnormal colonic epithelial proliferation. However, whether saturated or unsaturated fat is more harmful has not been categorically proven.

Vegetables and fruits are generally believed to confer a protective effect against CRC[2]. Anti oxidant effects due to vitamins (E, C and A) in the above have been implicated as protective, along with calcium intake. However, a recent meta-analysis on role of antioxidants for primary and secondary prevention of colorectal adenomas found no convincing evidence that antioxidant supplements have a significant beneficial effect on primary or secondary prevention of colorectal adenoma[24].

A recently concluded, eighteen-year trial has shown that consumption of caffeinated coffee or tea with caffeine was not associated with incidence of colon or rectal cancer, whereas regular consumption of decaffeinated coffee was associated with a reduced incidence of rectal cancer by 52% in comparison to those who never had decaffeinated coffee[25].

Family History

About 15% of colorectal cancers have been demonstrated to have MSI (Micro satellite instability). The two best characterised familial syndromes, hereditary non polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) are autosomal dominant inherited disorders accounting for approximately 2% and 0.1to1% of all adult cases of colorectal cancers respectively.

HNPCC

HNPCC, sometimes referred to as Lynch syndrome, is characterised by a relatively young age (mean age at diagnosis, 45 years) of onset of predominantly right-sided colon cancer, as well as tumours in a variety of extracolonic sites such as endometrium, stomach, ovary,

urethra, skin and hepatobiliary/pancreas. HNPCC is also relevant to paediatric gastroenterology practice because children as young as 9 years have been reported with underlying colorectal cancer and germ-line mutations of mismatch repair genes. Lynch syndrome is perhaps the most prevalent type of hereditary predisposition to cancer, occurring in about 1 or 2 of 1000 people[26]. The syndrome is neither common nor rare. The diagnosis of this hereditary disease has important implications for the treatment of the patient and of each of the patient's first-degree relatives. It appears that the progression from adenoma to carcinoma occurs substantially more rapidly in patients with Lynch syndrome than in patients with sporadic colorectal cancer – a finding that necessitates more frequent colonoscopic surveillance for patients with Lynch syndrome[27]. An important and unique aspect of this syndrome is that phenotypic markers in the tumour can identify most cases, something not possible for most other types of hereditary cancer.

The colorectal cancers in more than 95% of patients with Lynch syndrome have a mutational signature called micro satellite instability (MSI). This characteristic signature is historically important because micro satellite instability provided the crucial link to the genetic basis of the disease. Reference research laboratories can detect microsatellite instability, but its recognition is probably not within the grasp of most district general hospitals. Immunohistochemical analysis to detect DNA mismatch-repair proteins can be performed in most pathology laboratories, and with some training (which is essential), it is possible to identify about 95% of colorectal cancers associated with Lynch syndrome by demonstrating the absence of DNA mismatch-repair proteins in the tumour.

Nearly all HNPCC-associated tumours exhibit high-frequency microsatellite instability, manifested by expansion or contraction of mono- or dinucleotide DNA microsatellite repeats in DNA extracted from neoplasms [28]. The genetic basis for HNPCC is germ-line mutations of mismatch repair genes, predominantly MLH1 and MSH2 [29;30], with MSH6, PMS1 and PMS2 mutations accounting for a small number of cases [31;32]. Inherited germ-line mutations of mismatch repair genes are found in up to 50% of HNPCC subjects from families meeting the Amsterdam criteria (Table 2).

The identification of patients with Lynch syndrome is one of the important objectives in the management of colorectal cancer, but it is impractical to test every patient with the disease for these mutations. Comprehensive testing for mutations in DNA mismatch-repair genes costs about £2,000, and even thorough testing misses some mutations. For these reasons, clinical investigators have attempted to develop algorithms to identify patients who should undergo rigorous testing to find the 3 to 4 cases of the Lynch syndrome that lurk among every 100 cases of colorectal cancer[33].

	Name	Criteria
1	Amsterdam Criteria	1. Three relatives with colorectal cancer (CRC), one of whom is a first-degree relative of the other two. 2. CRC involving at least two generations; one or more CRC cases diagnosed before the age of 50.
2	Modified Amsterdam Criteria	1. Very small families, which cannot be further expanded, can be considered as HNPCC even if only two CRCs occur in first-degree relatives; CRC must involve at least two generations, and one or more CRC cases must be diagnosed under age 55. OR 2. In families with two first-degree relatives affected by colorectal cancer, the presence of a third relative with an unusual early onset neoplasm or endometrial cancer is sufficient.
3	Amsterdam 2	Three relatives with an HNPCC associated tumour (CRC, endometrial, small bowel, urethra, or renal pelvis), one of whom is a first-degree relative of the other two; involving at least two generations; one or more cases diagnosed before the age of 50.
4	Bethesda	1. Subjects with cancer in families that fulfil Amsterdam criteria. 2. Subjects with two HNPCC related cancers, including synchronous and metachronous CRCs or associated extracolonic cancers. 3. Subjects with CRC and a first-degree relative with colorectal cancer and/or HNPCC related extracolonic cancer and/or colorectal adenoma; one of the cancers diagnosed at age <45 years and the adenoma diagnosed at age <40 years. 4. Subjects with CRC or endometrial cancer diagnosed at age <45 years. 5. Subjects with right-sided CRC with an undifferentiated pattern (solid/cribiform) on histopathology diagnosed at age <45 years. 6. Subjects with signet-ring-cell-type CRC diagnosed at age <45 years. 7. Subjects with adenomas diagnosed at age <40 years.
5	Edinburgh Protocol	http://www1.hgu.mrc.au.uk/Softdata/MMRpredict.phpPr/(1-Pr) = 1.39 x 0.89(^{AGE})) x 2.57(^{SEX})) x 4.45(^{LOCATION})) x 9.53($^{SYN/MET}$)) x 46.26(^{CRCFH})<50) x 7.04(^{CRCFH}) greater/equal 50) x 59.36(^{ECFH})). Barnetson R A et.al[33]

Table 2 Various criteria for HNPCC syndrome.

FAP

Familial adenomatous polyposis occurs in approximately one in 10 000 live births. The classical diagnosis is based on there being more than 100 adenomatous polyps seen throughout the large bowel. The diagnosis may also be made from the family history plus/minus a positive gene test, with or without a particular number of adenomas being present. Familial adenomatous polyposis affects all three germ layers of the body. The endodermal manifestations, other than those of the large bowel, include polyps of the duodenum and small bowel, with a lifetime risk for small bowel carcinoma of 5–10%[34]. Gastric fundic gland polyps occur in approximately 50% of FAP patients[35].

Manifestations within the mesoderm include desmoid tumours. These occur in 0.03% of the non-FAP population[36], but in up to 32% of those with FAP[37]. They are a form of fibromatosis, arising within the peritoneum, the retroperitoneum or the abdominal wall.

Ectodermal manifestations include congenital hypertrophy of retinal pigment epithelium, found in 75–80% of FAP individuals and epidermal cysts, which may be multiple and found at a young age[36].

Mutations in the adenomatous polyposis coli (APC) gene on the long arm of chromosome 5 (5q) cause the syndrome. The protein product of this gene acts as a tumour suppressor gene. It is inherited in an autosomal dominant fashion, with almost complete penetration.

Most who carry FAP will have colorectal polyps and cancer by the age of 40 years. Genetic testing of family members with a positive family mutation should start from the age of 10–12 years. If a family member tests positive, prophylactic surgery is offered. If a family member tests negative (i.e. no mutation found) for the family's APC mutation, their risk falls to that of the general population. If the family mutation is not known, then yearly flexible sigmoidoscopy is recommended from the age of 10–15 years, until the age of 35 years. After this, the risk diminishes with age, but regular endoscopy should continue, at least every 3 years.

Upper gastrointestinal endoscopy is recommended for duodenal polyposis and computed tomography scanning in conjunction with magnetic resonance imaging is considered an effective method of screening for, and monitoring of, desmoid tumours.

Truncating germ-line mutations in the APC tumour suppressor gene are detectable in more than 80% of patients with classic FAP. Duodenal polyposis and desmoid disease remain major clinical challenges in the management of this condition.

Attenuated FAP

Attenuated FAP (AFAP) is characterised by the development of <100 polyps that tend to cluster in the proximal colon, with an older age of onset, and malignant transformation occurring 10 to 20 years later than classic FAP. Genetic testing should be considered in a person who exhibits typical FAP and also in
persons with as few as 10 adenomas because of the possibility of AFAP[38]. Until recently, no other genetic causes had been described for the remainder of patients with classic or attenuated polyposis.

Pre cancerous conditions

APC I1307K polymorphism within ethnic groups

This polymorphism is 30 times more likely to mutate, making the patient more susceptible to colorectal cancer, but at a level much lower than for FAP patients. In one study, the mutation was found in 6.1% of all Ashkenazi Jews tested, in 10.4% of Ashkenazim with colorectal cancer, and in 28% of Ashkenazim with colorectal cancer and a positive family history of colorectal cancer[39].

Gryfe et al. showed that the APC I1307K variant leads to increased adenoma formation and directly contributes to 3 -4% of colorectal cancer cases in Ashkenazim[40].

Other studies have shown this mutation to be uncommon or absent in different populations. Testing for this change outside the Ashkenazi population is therefore unlikely to be of clinical use.

Juvenile Polyposis

This is defined as the presence of more than five juvenile polyps of the colon, and/or juvenile polyps throughout the gastrointestinal tract, and/or any number of juvenile polyps in a patient with a family history of juvenile polyposis[36]. It may present with rectal bleeding in childhood. Juvenile polyposis is thought to be inherited in an autosomal dominant fashion.

The polyps are hamartomas, which may harbour some areas of dysplastic or adenomatous tissue. Endoscopy and polypectomy are required and, in some situations, colectomy and ileorectal anastomosis are necessary. Patients with isolated colorectal juvenile polyps in the absence of juvenile polyposis do not require surveillance.

Peutz–Jegher's syndrome

This is an autosomal dominant inherited disorder characterised by mucocutaneous melanin deposition, intestinal polyposis and an increased risk of cancer, both intestinal and extra-intestinal. The polyps, which can be found anywhere from the stomach to the rectum, are usually hamartomas, with most occurring in the small bowel.

The classical acute presentation is one of abdominal pain with intestinal obstruction, bleeding, anaemia or malignancy, in any combination.

Surveillance in these patients is directed towards the prevention of multiple laparotomies and the prevention or early detection of malignancy. One protocol uses yearly blood tests for haemoglobin and bilirubin and abdominal ultrasound, biennial (i.e. once every two years) 'top and tail' endoscopy, with snare polypectomy and biennial small bowel series.

The role of video-capsules remains to be determined. If a polyp of greater than 15 mm is seen on small-bowel radiology and is not accessible by standard endoscopic techniques, laparotomy is recommended. On-table enteroscopy should be performed when a laparotomy is carried out for any reason, as this has been shown to prevent the complications of small-bowel polyps, which include intussusceptions, bleeding and repeated laparotomies. Females may be offered yearly pelvic ultrasound from age 18 years, biennial cervical smears (both ecto and endocervical) and breast imaging every 5 years, from age 25 years. Males should have yearly testicular ultrasound until puberty, or in the presence of feminising features[41].

Hyperplastic polyposis syndrome

This syndrome is defined as: (i) at least five histologically diagnosed hyperplastic polyps proximal to the sigmoid colon, of which two are > 10 mm in diameter; or (ii) any number of hyperplastic polyps occurring proximal to the sigmoid colon in an individual who has a first-degree relative with hyperplastic polyposis; or (iii) more than 30 hyperplastic polyps of any size, but distributed throughout the colon.

Regular colonoscopic screening is recommended with polypectomy. Colectomy should be considered if there is difficulty with surveillance as a result of the large number of polyps and/or an advanced degree of dysplasia within the one or more polyps. A hyperplastic polyp to adenoma to carcinoma sequence has been postulated[42;43].

Genetics

It is now an accepted tenet in cancer biology that malignancy arises as a result of environmental factors on an appropriate genetic background. In colorectal cancer, the most commonly affected gene is APC, the gene which, when mutated in the germline, is responsible for FAP. Mutations in this gene occur early in the adenoma-carcinoma sequence and, when all forms of silencing of this gene is taken into account, abnormalities in APC appear to occur in virtually all colorectal neoplasms[44].

Another important gene is the K-ras, mutations of which are seen in almost equal numbers in adenomas and carcinomas, although not as frequently as APC mutations[44]. The K-ras protein is an important early step in the activation of a kinase-signalling pathway, which ultimately leads to changes in the nucleus favouring cellular proliferation. When the K-ras gene is mutated the protein becomes constitutively active, thereby, driving the cell towards uncontrolled proliferation.

Finally, the p53gene (which is the most commonly mutated gene in all human cancers) appears to play an important role in colorectal cancer, being abnormal in over 50% of invasive CRC. However, it only appears late in the adenoma-carcinoma sequence and is mainly seen in large adenomas and invasive carcinomas[45].

Possible roles of other etiological factors

A small study carried out in Turkey on 73 colorectal cancer patients with age and sex-matched controls revealed a non-significant difference in Bacteroides fragilis bacteria in the stool specimens in both cohorts. However, DNA extraction studies showed over 38% of CRC patients had an enterotoxoginic strain of Bacteriodes fragilis (bft gene) compared to 12% in the control group. The paper definitely admits a weakness in the study design due to the small number of cancers studied and not accounting for other factors implicated in etio-pathogenesis of CRC 46.

1.3 Colorectal Symptoms And Colorectal Cancers

Some colorectal cancers can present prior to the onset of any symptoms. This has been noted most in studies from the USA, varying from 5% to 20% in various hospital series[47-55].

These cancers have usually been detected through a screening procedure in those recognised to be at additional risk, such as those with a family history of colorectal cancer, or those with inflammatory bowel disease. With the steady increase in screening for colorectal cancer, the pattern of presentation is changing towards a higher proportion of asymptomatic cancers. Despite these changes, the majority of patients with colorectal cancers in the UK present with symptoms to their GP, and this is likely to continue to be the case for the foreseeable future[53;56;57].

At the other end of the spectrum, some colorectal cancers present with surgical emergencies, principally obstruction or perforation; these account for 3-21% of hospital series, with UK figures among the highest in similar societies[50;53;55;58-60]. Most of the emergency presentations have symptoms for a short duration; however, some studies quote a longer duration of symptoms[59;61].

Colorectal cancer can present in many different ways, and although many symptoms are associated with it, few if any are unique. Symptoms can occur in isolation or, more commonly, as clusters. Many studies have been done to identify high-risk symptom clusters, which would have higher probability of malignancy.

While this may identify subgroups of patients with a high chance of colorectal cancers, studies have shown that CRC may present as asymptomatic for a long period, eventually presenting with disseminated disease. Similarly, the absence of high-risk symptom clusters does not rule out the presence of CRC; however, 85% of CRCs referred to secondary care Outpatients have been shown to have one or more high-risk symptoms[62].

Colorectal cancer can present at any stage of the disease, from the in-situ stage within an adenomatous polyp to metastatic disease. Unfortunately the presenting signs and symptoms do not echo the stage of the disease. Observations on the predictive value[1] of the symptoms of disease can be seriously biased by 'selection phenomena'. This selection bias may occur from the general population, via consultation behaviour, the diagnostic and therapeutic activities of the GP, or by referral.

[1] Sensitivity is calculated as the proportion (or percentage) of malignancies correctly diagnosed, while specificity is the proportion (or percentage) of non-malignancies correctly diagnose. Positive predictive value is the proportion of positive diagnoses that correctly identify a malignancy, and negative predictive value the proportion (or percentage) of negative diagnoses that correctly exclude one.

Diagnostic research in secondary care often ignores this temporal factor. In hospital settings patients attend the clinic on a specific date and, based on this assessment supplemented with appropriate investigations, are provided with a 'diagnostic label'. In secondary care the emphasis is on making a clear and prompt diagnosis in a patient already sifted by primary care. However, it has been observed that the general practice patients often present early in the course of an illness when typical symptoms and signs are absent and, as the condition evolves, GPs may rely more on assessment and assimilation of information gained over a period of time (persistence or changes to the symptoms). It has been shown that significant symptoms (or clusters of symptoms) developing per unit time are often useful diagnostic tools in the general practice setting[63].

It is important, in advising on the management of the primary symptoms of bowel cancer in primary care, to take notice of the fact that the predictive value of these symptoms in this setting may be quite different to that in the community and in hospital practice[64].
In order to devise efficient decision-support software in primary care for colorectal referrals to secondary care, it is very important to take account of the current evidence base for prevalence, the positive predictive value (PPV) of symptoms and signs in isolation and combinations at various levels.

1) Prevalence and PPV of symptoms or signs in the general population.
2) Prevalence and PPV of symptoms and signs in patients who consult GPs.
3) Prevalence and PPV of symptoms and signs in the referred population.
4) Prevalence and PPV of symptoms and signs in the cohort investigated in secondary care.

Most literature focuses on colorectal cancer, and the PPV and prevalence estimates are for CRCs rather than for benign conditions. However, this information indirectly helps in sub-categorising benign conditions. There are definite gaps in the current literature with regard to prevalence, PPV and NPV estimates for the whole spectrum of colorectal symptoms and signs, and this overview is by no means exhaustive and complete.

In primary care, symptoms with a >1% PPV have been considered by most researchers to be at a significant level for referral to secondary care (Personal Communication, William Hamilton, Bristol).

1.3.1 Change In Bowel Habit (CIBH)

The nature of the change in bowel habit can be described in many ways, for instance changes in, frequency of defecation, consistency of stool, shape of stool and difficulties in evacuation with a feeling of incomplete emptying. It is often cryptically described as a

change to constipation or diarrhoea[65-75].

In the UK a 'change in bowel habit' specifically in the context of CRC, refers to loose stools or higher frequency of bowel movement than is normal for a person, persisting for 6 weeks, in those over 60 years of age[76].

A change in bowel habit is thought to be due to the obstructive effect a tumour has on the bowel lumen and is less frequently noted in right-sided tumours where the bowel content is more liquid. Various studies recorded the nature of the change in bowel habit in terms of changes in frequency of defecation and consistency of the stool[50;61;69;71;77-80]. These showed that changes to looser stools and/or increased frequency of defecation occurred in 60-91% of patients with distal cancers and 40-61% of patients with proximal cancers. In these studies it was unusual for patients to have alternating constipation and diarrhoea or the common form of constipation i.e. decreased frequency of defecation and harder stools. Patients with complete intestinal obstruction usually had a change in bowel habit of short duration before presentation.

In major studies carried out in general practice, diarrhoea or a change in bowel habit to looser stools and/or increased frequency in defecation, was commonly associated with rectal bleeding in patients with bowel cancer[61;81-84].
Although constipation is not described as a high-risk criterion by the Department of Health Guidelines[85], recent work in primary care points towards constipation as a significant optional criterion for referral, both alone and in combination with other symptoms[61].

	Prevalence	Incidence	PPV for CRC	NPV for CRC
General Population	4% to 6%(Diarrhoea) 8.6% & 9.7%(Any CIBH)†[86]	0.98%[83] (40 to 89 years age group) Any CIBH	N/A	N/A
Primary Care	6% (Any CIBH) †[86] 1.5%[87] (CIBH reported in Primary Care)	N/A	*1.5%[61] (CI 1-2.2) {0.63%(40-69yr) 1.7% (70 or Over)} 3%[87]	N/A
Referred Group	40%(Diarrhoea)[79] 13%(Constipation)[79]	73%[79] (Any CIBH)	5.0%[79] (any CIBH, Diarrhoea 8% Constipation 1.4%)	N/A
Secondary care	N/A	N/A	1:17 [78] (Isolated CIBH)	N/A

Table 3 The prevalence and incidence of CIBH, Positive Predictive Value (PPV), and Negative Predictive Value (NPV) for change in bowel habit for CRC. Any CIBH refers to diarrhoea or higher frequency than normal for a person. refers to either constipation or diarrhoea or both; Isolated CIBH

† Refers to change in frequency and change in consistency respectively in the last six months.

* PPV for CRC in patients in primary care with diarrhoea, presenting at least twice to their GP with this symptom in the context of a background risk of 0.25%.

1.3.2 Rectal Bleeding

This is one of the commonest and maybe the earliest symptom for colorectal cancer, but most commonly arises from a benign source[88;89]. It is generally thought to be a symptom of early rather than late colorectal cancer, either alone or in combination with other symptoms[90;91].

Prevalence

The prevalence of rectal bleeding in the community has been primarily studied using validated questionnaires in the general population. Crossland and Jones demonstrated a 24% overall prevalence and 19% prevalence of rectal bleeding in the previous year in those 20 years of age and above[92]. A population study (predominantly Caucasian, 20 to 64 years) from the United States quotes a 15.5% prevalence for rectal bleeding[93]. In a survey of industrial employees older than 40, a 12% prevalence was noted for rectal bleeding and a 15% lifetime prevalence in another study[94;95]. In Portsmouth, UK, a prevalence of 18% was noted for rectal bleeding in the previous year in those 16 years and over[96].

All these studies have also demonstrated higher prevalence of rectal bleeding in younger age groups[88;92-98].

Various studies have looked at the consultation behaviour in the general population and the interface with primary care. Crossland and Jones showed a 41% consultation rate, and non-consultation was found to correlate with a lack of “perception of the seriousness of the symptom”. They were usually younger people, and those having fresh bleeding as opposed to blood mixed with stool[92]. Another study of rural and semi-urban populations of adults in the UK demonstrated a 54% consultation rate. Bleeding into the pan rather than blood on the toilet paper prompted consultation[86]. However, lower consultation rates of 14% and 28% have been noted in similar studies performed in the USA and UK[93;96]. Only 7% of patients with rectal bleeding in a population study were referred to secondary care for investigation[96]. However, 30% to 50% of patients with rectal bleeding are referred from primary care to secondary care[93;96].

Incidence

The reported incidence of rectal bleeding in the general population can vary between studies from 8%-16% in middle aged and elderly people[98;99]. Fijten et al derived a figure of 20% of the adult general population reporting rectal bleeding in the previous year, and 2% in the previous two weeks[88].

PPV

It has been estimated that the predictive value of rectal bleeding for colorectal cancer is less than 1 in 1000 in the general population, approximately 2 in 100 in general practice and up to 36 in 100 referred patients[88]. However, a different estimate, 1 in 700 in the community [96] to 1 in 30 in primary care[100] and 1 in 16 in a hospital setting[101], can also be derived from three separate studies.

In a study of 269 patients aged between 18 and 75 years, presenting with rectal bleeding to their General Practitioner in a one year time period, 20% of those in the 60-75 year age group had colorectal cancer, compared to only 2% in the 50-59 year group and none in the younger age groups. In this same study, the odds for colorectal cancer were in favour of male patients over 60 years[82]. However, in an earlier study of patients over 40 years old attending their GP with first episode rectal bleeding, a high prevalence of polyps (24%) and colorectal cancer (10%) was observed, and 67% of cancers were localised to the bowel wall. The other important finding was the high prevalence of haemorrhoids (63%) concurrent with colonic lesions in the same cohort[89].

	Prevalence	Incidence RB	PPV for CRC	NPV for CRC
General Population	15% of adults (Lifetime) RB[94] 1:420[102] (CRC prevalence in RB)	1.6%[83],	<1:1000[88]	N/A
Primary Care	1:116[102] (CRC prevalence in RB)	2 - 8:1000/yr[84;88;103]	~2to3.3: 100[82;88] 7:100[104]	N/A
Referred Group	1:32[102] (CRC prevalence in RB)	0.8:1000/yr[88]	~36:100[88]	N/A
Secondary care	55% to 80%(Distal CRC)[69;71;78;80;105]}, 5%to15%(Proximal CRC)[69;71;80]	N/A	1:18[78]	N/A

Table 4 The prevalence and incidence of rectal bleeding (RB), PPV, NPV for colorectal cancer (CRC) in patients presenting with rectal bleeding. N/A: Not available

Characteristics of Bleeding

Colour of blood passed can be inappropriately interpreted by patients[106], and use of a colour card has shown 70% having bright red, 22% dark blood and 8% darker burgundy or maroon. The majority of bright red bleeding (83%) was from the distal 60 cm; however, significant pathology would have been missed with isolated flexible sigmoidoscopy (20 of 217 patients had a more proximal lesion including 8 CRCs)[106].

In primary care, blood mixed with the stool and dark blood, or both combined, were associated with a greater likelihood of CRC (Likelihood Ratio-3.0) in a community-based flexible sigmoidoscopy trial[107]. Blood mixed and/or coating stool (odds of 8) has also been shown to be associated with a higher probability of CRC in primary care[82]. However, a recent paper from primary care fails to support the significance of dark blood for cancer, significant polyps or colitis compared to bright red bleeding, although this could possibly be due to the low number of patients included in the analysis, not being representative of a true sample and results opposite to larger series published (six patients out of 319 patients with rectal bleeding and over 34 years of age)[81]. However rectal bleeding of any nature in primary care is considered a 'mandatory referral symptom', in a large retrospective case control study requiring investigation in secondary care[108]. This would be however considered a too cautious approach by some[62;102;109].

A slightly different picture is seen in patients referred to secondary care. Patients with a history of dark and bright blood combined, had a higher PPV and relative risk (RR) of CRC (PPV-13.2%, RR-3.53) than dark blood (PPV-10.6%, RR-2.65), and bright blood (PPV-4.3%, RR-1.08). The same secondary care study noted blood mixed in stool to have a higher PPV of 11.0% and RR-3.35, compared to blood separate from stool (PPV of 3.4%, RR-0.77)[79]. Bright red blood streaking stool has been shown to have a positive predictive value of 96% for an anorectosigmoid bleeding site[106] , while bright red blood dripping into the pan towards the end of defecation and on the toilet paper is more commonly due to haemorrhoids. In spite of conflicting studies on the most appropriate investigation for rectal bleeding, it is suggested from studies in the USA[110] that colonoscopy is the most complete option with high negative predictive values in those over 40 years. This is regardless of the pattern of bleeding and presence or absence of other symptoms and signs. A contrary view is held in the UK and flexible sigmoidoscopy remains the mainstay of investigation[111;112].

1.3.3 Weight Loss

Two studies have quoted a general population prevalence of unintentional weight loss of 2.3% and 3.3%[86;113]. There is still confusion regarding the definition of clinically relevant weight loss. However, loss of 5% of the body weight in 6-12 months is considered significant.

In CRC and in serious benign conditions such as inflammatory bowel disease, patients can lose weight significantly, but this is usually manifested later on {median – 27 weeks (range 9-42)}[50]. Majumdar et al in their study of 194 patients with CRC recorded weight loss in 39% of patients. There was a trend towards a higher incidence in proximal CRC (46%) than in distal CRC (34%), but this did not achieve statistical significance[50].

Selvachandran et al derived a PPV for weight loss and CRC of 9.4% in the referred

population to secondary care. However, a much lower figure of 1.2% is found in the unselected primary care population[61;79].

Interestingly, the PPV of weight loss in combination with rectal bleeding (4.7%), diarrhoea (3.1%, CI-1.8% to 5.5%) and constipation (3%, CI 1.7% to 5.4%) are much higher than isolated weight loss for CRC in an unselected primary care population with a background incidence of 0.25%[61].

1.3.4 Abdominal Pain

15% to 30% of the general population have experienced this symptom in the past year[86;94;98;114;115]. This may be part of irritable bowel syndrome, which is more common in younger age groups and is usually associated with diarrhoea at the outset[116]. Irritable bowel syndrome usually recurs over long periods of time[117;118]. Numerous medical and surgical pathologies give rise to abdominal pain. The symptom in isolation has been considered to lack sensitivity or specificity for CRC and is not included in the Department of Health referral criteria[119].

However, various studies in primary and secondary care have shown abdominal pain to be present in 45% to 90% of patients with proximal CRC, and 10% to 50% of patients with distal CRC[120].

	Prevalence	Incidence	PPV for CRC	NPV for CRC
General Population	17.2%(Previous six months) to 25% UK in previous year[86;94;115]	N/A	N/A	N/A
Primary Care	15.1%† (clinically relevant population)[86]	0.4% with abdominal pain had CRC in a years time period[121]	*3%(CI 1.8 to 5.2%)	N/A
Referred Group	N/A	54%[79]	2.7%[79]	N/A
Secondary care	N/A	N/A	N/A	N/A

Table 5 The prevalence and incidence of abdominal pain and the PPV and NPV of abdominal pain for CRC.

* PPV of abdominal pain for CRC in unselected population for patients presenting with repeat episodes to the GP[61].

† Refers to the population who attend or plans to attend their doctor for abdominal pain or discomfort.

Even though the non-specific feature of abdominal pain is well recognised, a recent study in a primary care population categorised 'abdominal pain with no clear diagnosis' and rectal bleeding as two symptoms, which could be significant prediagnostic features of

CRC, noticed up to 180 days before presentation in secondary care[61]. Similarly, a combination of abdominal pain with weight loss (PPV-3.4%), or rectal bleeding (PPV-3.1%), or diarrhoea (PPV-1.9%), resulted in an increased PPV for CRC in the primary care population[61].

Signs of Colorectal Cancer

1.3.5 Palpable Mass (Rectal And Abdominal)

Two commonly described masses in relation to CRC are the palpable rectal tumour and palpable right iliac fossa abdominal mass. The accuracy of rectal examination in general practice has rarely been studied. In one series, GPs had an 82% accuracy with a false negative rate of 18%[122]. The ability to differentiate a true intraluminal rectal mass from cervix, fibroid uterus, and other pelvic pathology would help to reduce false positives.

A recent study in general practice of patients over 34 years old with rectal bleeding, showed that 36% (4 in11) of rectal cancers were palpable on digital ano-rectal examination[81]. However, in a previous study in primary care of 290 consecutive patients with overt rectal bleeding, aged between 18 and 75 years, only 77% had a digital ano-rectal examination by the GP and one rectal cancer was found (PPV of 100%)[82]. A more realistic figure in general practice, with a background CRC risk of 0.25%, is a PPV for abnormal rectal examination of 4% (CI 2.4% to 7.4%). In this same study 14.6% (51 out of 349 CRC) had palpable rectal disease, compared to 0.8% (14 out of 1744 age-matched controls)[61].

There is only one relevant study which quotes 80-90% of patients with lower gastrointestinal symptoms having abdominal examinations performed in general practice[82].

	Prevalence	Incidence	PPV for CRC	NPV for CRC
General Population	N/A	N/A	N/A	N/A
Primary Care	N/A	N/A	*4%(CI 2.4% to 7.4%) (Rectal mass)	N/A
Referred Group	N/A	N/A	N/A	N/A
Secondary care	N/A	40-80% of rectal & 20-40% sigmoid, 40-55% of proximal cancers [123]	~100% for intra rectal mass visualised.	N/A

Table 6 The prevalence and incidence of rectal and abdominal mass and the PPV and NPV of palpable mass for CRC.

*In unselected population with background prevalence of CRC of 0.25%[61].

1.3.6 Iron Deficiency Anaemia (IDA)

The World Health Organisation defines IDA as a haemoglobin below 13gm% in males over 15 years and below 12gm% in non-pregnant females over 15 years[124].

After aspirin/NSAID use, colorectal cancer, gastric cancer and coeliac disease are the most common gastrointestinal causes of iron deficiency anaemia[125].

Causes	*Percentage*
1. Occult GI Blood Loss	
Common	
Aspirin/NSAID use	10–15%
Colonic carcinoma	5–10%
Gastric carcinoma	5%
Benign gastric ulceration	5%
Angiodysplasia	5%
Uncommon	
Oesophagitis	2–4%
Oesophageal carcinoma	1–2%
Gastric antral vascular ectasia	1–2%
Small bowel tumours	1–2%
Ampullary carcinoma	<1%
Ancylomasta duodenale	<1%
2. Malabsorption	
Common	
Coeliac disease	4–6%
Gastrectomy	<5%
H. Pylori colonisation	<5%
Uncommon	
Gut resection	<1%
Bacterial overgrowth	<1%
3. Non-GI blood loss	
Common	
Menstruation	20–30%
Blood donation	5%
Uncommon	
Haematuria	1%
Epistaxis	<1%

Table 7 Causes of IDA with prevalence as % of total[124].

Iron deficiency anaemia is a classic pointer to CRC[67], demanding urgent investigation[126]. It is present in 11–57% of cancers[50;80;127], and is particularly suggestive of right-sided tumours (65 to 80% have IDA)[128-130].

Various studies have used different values of haemoglobin (Hb) and other blood indices, and any derivation of point estimate should bear this in mind. The UK CRC referral guidelines use 11gm% and 12gm% for females and males respectively[131].

The PPV of IDA (Hb < 7.5mmol/L and < 8.5mmol/L) for CRC in adults presenting with

rectal bleeding in primary care study was14%, though this high value could be accounted for by very low Hb values considered in the analysis[82]. A recent UK retrospective study of 2600 IDA patients in secondary care has reported interesting results, especially in the light of current BSG guidelines. The number needed to investigate (NNI) and pick up a CRC at a curable stage was 38 colonoscopies, compared to 527 gastroscopies to pick up one curable, upper-GI malignancy (stomach or oesophagus). Potentially curable gastrointestinal malignancy was diagnosed over 13 times more frequently using colonoscopy or barium enema compared to gastroscopy. This favours investigation of the lower GI tract first, or performing both colonoscopy and gastroscopy simultaneously if the facilities exist[132].

Measurement of serum ferritin has been proven to be the most accurate, non-invasive predictor of IDA[133;134], and a very recent study has noted a 5-fold increase in the prevalence of advanced colorectal neoplasm, 7.9% in those with a ferritin ≤50ng/dl, and 7.2% when the ferritin is 51to100ng/dl, compared to 1.2% in non-anaemic individuals. There is a strong recommendation for colonoscopy in those with a ferritin less than 100ng/dl, especially men[135].

	Prevalence	**Incidence**	**PPV for CRC**	**NPV for CRC**
General Population	1% for IDA in UK population[136]	2.4%[83]	N/A	N/A
Primary Care	20% of men with Hb≤12gm% have CRC[130]	N/A	7.4%[136] Or 1-3%[83]	N/A
Referred Group	N/A	N/A	N/A	N/A
Secondary care	15% in CRC[62]	60% of CRC[129]	11%[137](Hb12.4gm%&10.6gm%)	N/A

Table 8 The prevalence and incidence of iron deficiency anaemia and the PPV and NPV of IDA for CRC.

1.3.7 Acute Presentation

Acute admissions account for 25-40% of colorectal cancer patient presentations in secondary care. This is commonly due to small bowel obstructive symptoms and signs secondary to a caecal cancer, or a large bowel obstructive picture secondary to a distally located cancer, which is more common. Acute presentation with rectal bleeding or anaemia is seen in a few patients. Occasionally an acute presentation may be with peritonitis, secondary to perforation.

With better recognition of the significance of symptoms at first presentation, it would be possible in some cases to refer for elective investigations prior to development of acute symptoms[61;138;139]. An immediate survival advantage could be anticipated by treating patients in a non-acute setting.

1.3.8 Metastatic Disease At Presentation

Other less common presentations both in primary care and secondary care are patients with palpable liver metastasis, general malaise and weight loss from a colorectal primary. These account for 5-10% of presentations to secondary care[140].

1.3.9 Combinations Of Symptoms And Signs In Colorectal Diseases

Studies have tried to evaluate combinations of symptoms and signs in an attempt to derive models and significant predictive factors for cancer, polyps and IBD. Such studies have been carried out in primary care at the general practice level[81;82;141], in patients referred to secondary care and in studies in secondary care[50;78;79;142;143]. For instance, a recent study in primary care has shown that the presence of two or more symptoms doubles the risk of CRC[83] and, in secondary care, a median of 3 symptoms (range 1-10) is noted for all CRC patients[50].

Primary Care

In one study, 14.5% of patients presenting with non-acute abdominal symptoms (lasting a minimum of two weeks or more) had organic pathology, and 2.6% (24/933) were neoplasms. When focussed on predicting neoplasms, the model consisted of five items: male sex, greater age, non-specific character to abdominal pain, weight loss (>1 kg in four weeks) and an erythrocyte sedimentation rate greater than 20mm/hour. These were described in primary care as “Signs of Alarm”[141].

Smith and colleagues have described in this study that patients reporting a specific character of pain, attaining pain relief after defecation, and of the female sex, were associated with irritable bowel syndrome[144].

The combination of rectal bleeding and a change in bowel habit to looser and/or more frequent stools has a higher PPV of 9.2, compared to rectal bleeding with no change in bowel habit[81]. Rectal bleeding and a change in bowel habit to looser and/or more frequent stools had a positive predictive value of 12.1, when compared to bleeding with change to decreased frequency of defecation and/or harder stool (2.8%). Various other studies quote significant associations between rectal bleeding and change in bowel habit[78;82;84;141;145].

Another significant association is rectal bleeding without perianal symptoms, with a PPV of 11.1% for CRC compared to rectal bleeding and presence of perianal symptoms (1.97%). Furthermore, rectal bleeding without perianal symptoms has a 31.7% positive predictive value for all colorectal cancer, polyps and IBD combined[81;96].

The same study[81] also shows no significant increased risk for cancer, polyps and IBD when abdominal pain accompanies rectal bleeding and a change in bowel habit. The complex of rectal bleeding with abdominal pain in a secondary care setting has previously been shown to have a low likelihood ratio[2] of 0.36(1:148 PPV) for colorectal cancer, compared to isolated rectal bleeding (1:18 PPV) with a likelihood ratio of 3.2[78]. The situation is, however, confusing, as blood mixed with stool, CIBH and abdominal pain have been associated with significant pathology in a separate study[145].

Earlier work in primary care using forward stepwise regression analysis revealed three variables significantly contributing to the prediction of presence or absence of cancer. These were age (Odds Ratio=8), change in bowel habit (OR=10) and blood mixed with stool or on stool (OR=8). These combined had a 97% discriminatory power in the area under the curve (AUC) analysis. This model resulted in 87% of patients with rectal bleeding being correctly predicted not to have colorectal cancer and reduced the need for further assessment[82].

In a separate study of patients consulting their GP with rectal bleeding, patients over 60 years and those with an associated palpable mass (PPV-31.5%), or weight loss (PPV-16%), or fatigue (PPV-7.1%) had a higher chance of harbouring CRC. The same study failed to show any association between rectal bleeding and abdominal pain (PPV-0%), but did with 'bowel spasms' (PPV-5.4%)[104].

Secondary Care

In the secondary care setting, various studies have tried to evaluate which symptom clusters are significant in predicting the site of cancer[50;78;79;142;143;146].

In 194 colorectal cancer patients studied, the most common symptoms were rectal bleeding (58%), abdominal pain (52%) and change in bowel habit (51%). In the same hospital series, faecal occult blood positivity (77%) and anaemia (57%) coexisted with theses symptoms[50]. Left-sided cancers rarely present as isolated bleeding and usually

[2] The likelihood ratio incorporates both the sensitivity and specificity of the test and provides a direct estimate of how much a test result will change the odds of having a disease. The likelihood ratio for a positive result (LR+) tells you how much the odds of the disease increase when a test is positive. The likelihood ratio for a negative result (LR-) tells you how much the odds of the disease decrease when a test is negative.

have one or more associated bowel symptoms[147].

A prospective 12-year study has shown rectal bleeding with change in bowel habit and absence of perianal symptoms to have the highest PPV of 19.7; however, this only accounted for 31% of CRCs seen in secondary care[146].

1.3.10 Family History

Family history and Familial Syndromes

Some referrals from primary care to colorectal surgeons or gastroenterologists are of patients with a definite family history of CRC asking for advice or screening colonoscopy. Excluding the patients who meet HNPCC or familial adenomatous polyposis (FAP) criteria and other autosomal dominant genetic syndromes associated with colorectal cancer susceptibility, or those with mutations in CRC-susceptible genes, e.g. APC or DNA mismatch repair, there are two groups of the general population that merit screening colonoscopy[148].

1] People with a first-degree relative diagnosed with colorectal cancer aged less than 45 years.
2] Those with two first-degree relatives with CRC.

The suggested action in these patients includes referral to a clinical genetics service, especially if the above group has CRC in distant relatives.

Colonic evaluation preferably by colonoscopy is recommended between 35- 40 years, or at the time of consultation, whichever is later, and then a repeat colonoscopy at 55 years. Individuals with a normal study at age 55 have a lifetime risk of CRC that matches the population risk in general.

A predilection for right-sided CRC in those with family history renders flexible sigmoidoscopy an inefficient method of evaluation and barium enema with a targeted colonoscopy has been recommended as an alternative. There seems to be a particularly high risk of proximal lesions for women who have a family history.
Most important in defining the empirical risk for the general population is the current age of the patient whose risk is being considered. As shown in the table below, only patients with a first-degree relative affected by CRC under age 45, or those with two first-degree relatives with CRC, merit investigation. Since the population incidence of CRC is markedly skewed towards the elderly, even young people with a higher relative risk would still have a low absolute risk of CRC.

Risk Group	Lifetime risk of dying of CRC[149]
General population	1:50
Any family history of CRC	1:17
One first-degree relative <45 years	1:10
Two affected relatives (first-degree)	1:6

Table 9 Lifetime risk of dying of CRC based on family history

In addition, a large proportion of the population with lesser degrees of family history have an absolute risk that is less than the overall population risk. Referral pathways need to have strict guidelines to avoid a disproportionate increase in the colonoscopy workload.

The benefit of screening a population for familial CRC should outweigh the risk and cost involved. Some 4% to 7% of control cohorts report at least one affected relative, while the greater the number of affected relatives (particularly at younger ages), the greater personal risk of colorectal cancer.

The above-mentioned criteria do not apply to familial CRC as seen in HNPCC, Peutz Jegher's syndrome, FAP and other less common inherited CRC syndromes. The Incidence of CRC in these ranges from 10 to 100%. Well-defined clinical criteria or genetic mapping are required, and referral to a clinical geneticist if criteria are fulfilled. Screening for defective genes in family members is also advised followed by colonoscopy in those found to be susceptible.

In contrast to the above work on family history, risk and invitation for screening, very little study has been done regarding the presence or absence of family history in relation to the previously mentioned symptomatic populations (e.g. rectal bleeding, CIBH etc).

Fijten et al have looked at the relevance of family history in relation to patients presenting with rectal bleeding in general practice and surprisingly found a negative association between family history of abdominal disease and colorectal cancer. The relative risk of approximately 3 was considered too small to be found in the general practice population they studied[82]. The current Department of Health referral criteria do not include family history as a high-risk criterion. Unfortunately, there is no evidence base to assess its potential usefulness and more work needs to be done in this respect.

1.4 Investigations

Lower gastrointestinal symptoms and suspected iron deficiency anaemia in patients often need to be investigated and two main types of investigations are available: endoscopy (rigid or flexible sigmoidoscopy and colonoscopy) and imaging (barium enema and computed tomography, including CT colonography and MRI pelvis).

Each method of investigation has specific advantages and disadvantages, making it more or less appropriate for individual patients. The local availability of facilities, equipment, and skilled staff will inevitably influence the choice of investigations. However, with the upgrading of diagnostic services, the impact of these service variables is diminishing in most hospitals in the UK. This section on investigations tries to shed light on various

modalities of investigations and its relevance in the design of e-RP. Specifically in the design of e-RP, I have adopted the "straight to test" facility and hence the following sections on various modalities currently available.

Colonoscopy

This is the Gold Standard investigation for colorectal pathologies. Hospital episode statistics show that the use of both colonoscopy and flexible sigmoidoscopy has been rising each year since 1995/6. In 2000/1, there were 154,000 colonoscopies in England and 134,000 day-case flexible sigmoidoscopies. A typical Trust carried out between 500 and 1,000 colonoscopies and 400-800 flexible sigmoidoscopies per annum[150].

In an adequately prepared patient, colonoscopy provides a detailed assessment of the entire large bowel from anal verge to caecum; it also permits the removal of polyps, biopsy for histology assessment and taking photographs.

Some special uses of colonoscopy are highlighted below.

Use in follow up after primary treatment

Although there is no evidence that colonoscopic follow up improves survival, it does produce a yield of treatable tumours. It is recommended that once a "clean" colon is established, colonoscopy at five years after surgery and thereafter at five-yearly intervals up to the age of 70 is appropriate [151].

Family History

Colonoscopy is the method of choice for large-bowel screening for people at increased risk due to a family history and in view of the risk of lesions restricted to the proximal colon in a substantial proportion of cases.

Total colonic assessment is recommended at consultation about family history, or between the ages of 35–40 years, whichever is the later, and a repeat total colonic assessment at age 55 years. Polyps must be snared and histologically characterised. If adenomatous polyps are confirmed at either of these screening episodes, then adenoma surveillance guidance applies[152].

Colonoscopy forms the cornerstone investigation for right sided Colonic lesions and IDA and this is seen in the e-RP as 'straight to test'.

Flexible Sigmoidoscopy

Flexible sigmoidoscopy allows assessment of up to the last 60 cm of the large bowel (typically to the splenic flexure) after preparing the bowel with a phosphate enema. Flexible sigmoidoscopy is relatively quick and virtually risk-free, and is therefore the most appropriate initial investigation for the majority of patients with symptoms – notably rectal bleeding and/or change in bowel habit – that suggest possible lesions in the left colon or rectum.

The reach of the flexible sigmoidoscope is limited to 60 cm, but when neither cancer nor significant polyps are found in patients with these symptoms, and none of the symptoms or signs of right-sided disease are present, the probability of cancer is very low. A watch-and-wait strategy to see if symptoms resolve is therefore likely to be appropriate for low-risk patients.

Over a 15-year period, cancer was diagnosed in 5.6% of 16,487 patients who underwent flexible sigmoidoscopy for lower gastrointestinal symptoms in a district general hospital (DGH) outpatient clinic. In patients who had no other reason (e.g. iron deficiency anaemia) to suspect proximal cancer, and negative findings on flexible sigmoidoscopy, only 0.2% had cancer beyond the reach of the sigmoidoscope[153]. Flexible sigmoidoscopy has been included as 'straight to test' in the e-RP for patients with predominantly left sided colorectal symptoms.

Barium enema and plain radiographs

Barium enema is a well-established investigation for colorectal symptoms. It has the advantages of safety and availability, and there is no need for sedation, which means that patients can travel home alone after the procedure.

However, because barium enema on its own is a less sensitive diagnostic method than colonoscopy[154], a negative result cannot always be relied upon to demonstrate that the patient's symptoms are not due to colorectal cancer or polyps. The sigmoid colon due to redundancy and diverticular disease, caecum and ascending colon because of faecal residue and poor mucosal coating are the commonest areas where higher false negative rates can be expected[154;155]. Also, barium enema does not permit tissue diagnosis or polyp removal[155;156]. For these reasons, the use of barium enema is declining as the availability of colonoscopy and CT colonography increase.

Plain radiographs have a limited role in the investigation of colorectal cancer, although plain radiographs form a major part of the assessment of patients presenting acutely.

Signs on plain films that may be present in cases of CRC, include obstruction, soft tissue mass with distorted luminal shadow, calcification of the primary tumour or hepatic metastasis, and air in the bladder in the case of fistulating disease.

Computerised Tomography (CT) scan and CT Colonography

In recent years, the CT scan has been consistently used for staging local disease and distant disease in almost all units dealing with colorectal cancer. A policy of staging cancers preoperatively with chest, abdomen and pelvis high-definition scans has revolutionised treatment for CRC. There has been increased use of preoperative chemotherapy, and combined radical chemo radiotherapy where indicated, before definitive surgical excision of the tumour. CT scans also permit evaluation of recurrent or metastatic disease and may be used as an adjunct to guided percutaneous biopsy. A non-invasive mode of assessing the colon is CT colonography, which can match the sensitivity and specificity of colonoscopy especially in patients unfit for the latter test.

Magnetic Resonance Imaging (MRI)

The main role of the MRI is in the preoperative staging of rectal cancers[157;158]. This is particularly in relation to the assessment of the threatened circumferential resection margin, T stage and N stage of the tumour, and whether patients should be considered for primary surgery or preoperative chemo radiotherapy[159].

MRI is also increasingly being used to evaluate liver secondaries especially pre and post liver resection[160].

Positron Emission Tomography (PET scan)

Positron emission tomography (PET) scanning is an emerging technology, capable of identifying local recurrence, liver metastases and distant metastases in colorectal cancer[161]. In conjunction with other imaging modalities it may be helpful in assessing the extent of metastatic disease, and hence influencing decisions on patient management. The optimum role of PET scanning in relation to more established imaging methods is not yet clear. PET imaging facilities are currently only available in a few centres in the UK, although this situation is expected to change significantly over the next few years.

Faecal Occult Blood (FoB)

FoB testing has a debatable role as an investigative modality. It has a low sensitivity and specificity, resulting in large numbers of both false positive and false negative results. There is a risk of over-investigation or inappropriate reassurance.

However, in screening asymptomatic general populations, FoB testing has been shown to reduce mortality from CRC by 15-18% in randomised studies[48;51;162]. Recently,

immunohistochemical FoB has been shown to be more promising than the conventional guaic based FoB test kits in terms of detection rates especially for high-risk adenomas in a screened population[163].

Investigation Pathways

Patients presenting to General Practitioners with colorectal symptoms are often referred to secondary centres for further evaluation. Conventionally, consultants in clinics see patients and then selectively investigate further. The utility of a dedicated proctology clinic for colorectal patients with a one-stop investigation facility was possibly first demonstrated in 1993 in St. George's Hospital in London[164].

However, in the last decade there has been an increasing trend to send patients directly for investigations in secondary care[165-171] and this has been a significant move in reducing delays in cancer patient pathways. However, the onus is on the General Practitioner to triage and sort the patients into appropriate pathways and with appropriate urgency.
There are advantages and disadvantages to this referral process (see table below).

	Advantages	Disadvantages
Outpatient	Detailed history Patient asks questions	Wasted time if tests inevitable
Direct Investigation	Reduce waiting Free Outpatient slots	Unnecessary test Patient unable to ask questions

Table 10 Investigation Pathways: two sides of a coin

1.5 Screening

Intuitively, early diagnosis of cancer should be helpful, either in terms of a reduction in mortality or of morbidity. Indeed, the 'obvious' value of early diagnosis has meant that few studies have actually addressed whether it is indeed helpful. The only way of truly testing if early diagnosis does provide a benefit would be a randomised, controlled trial incorporating a deliberate delay in one arm of the trial. This would raise major ethical problems. Therefore, the evidence in favour of early diagnosis is mostly indirect and relates to screening or staging studies.
The intention of screening is to identify pre-clinical disease in a target population, the expectation being that identification and treatment of a condition at an earlier stage will

reduce morbidity and mortality. The World Health Organisation first published 10 general principles of screening in 1968, and they are as follows:

- The condition should pose an important health problem.
- The natural history of the disease should be well understood.
- There should be a recognisable early stage.
- Treatment of the disease in its early stage should be of more benefit than treatment started at a later stage.
- There should be a suitable test to detect the disease.
- The test should be acceptable to the population.
- There should be adequate facilities for the diagnosis and treatment of the abnormalities detected.
- For diseases of insidious onset, screening should be repeated at intervals, determined by the natural history of the disease.
- The likelihood of physical or psychological harm to those screened should be less than the likelihood of benefit.
- The cost of the screening programme should be balanced against the benefit(s) it provides.

Screening aims to detect cancer either by identifying cellular changes which may progress to cancer (as in cervical cytology) or by detecting the cancer when it is small (as in mammography). Two characteristics complicate the interpretation of screening trials. The first is that screen-detected tumours – which are generally smaller than those detected otherwise – may be biologically less aggressive than clinically detected tumours[172]. This is the length bias[173]. Secondly, by identifying cancers earlier, patients will apparently live longer after diagnosis, even if treatment had no beneficial effect. This is the lead-time bias[174].

1.5.1 Screening For Colorectal Cancer

Colorectal cancer screening shows benefit in terms of both early disease detection and consequent reduction in mortality[48;51;162]. Prevention or reduction in the long-term incidence of significant neoplastic lesions in the screened population has been achieved by identification and removal of pre-malignant adenomas[175]. There is good evidence that removal of colonic polyps reduces the incidence of colorectal cancer in the subsequent six years[176].

The focus of research efforts has been to find the best method of detecting such polyps, with the main options being faecal occult blood testing or regular flexible sigmoidoscopy.

With faecal occult blood testing, a relative risk reduction of death from colorectal cancer of 33% after 18 years of follow up has been reported from the USA[51;175], 30% from Denmark after 11 years[49], 16% in France after 11 years[177], and 15% after 8 years in the UK[48].

With flexible sigmoidoscopy, two case control studies reported reductions in the relative risk of death from colorectal cancer after flexible sigmoidoscopy[178;179], and a large UK prospective study of flexible sigmoidoscopy has reported its preliminary results[54;180]. Nearly half a million patients aged 50-69 were offered faecal occult blood testing; 57% accepted, 2% had a positive test, and 11% of those with positive tests had a colorectal cancer. Colorectal Cancers diagnosed by screening have a better Duke's staging[49;51;54;181], and as screening increases, fewer colorectal cancers present as an emergency[182].

In colorectal cancer, like lung cancer, one of the main obstacles to improving survival is the high number of patients presenting with advanced disease. Studies so far suggest that regular faecal occult blood screening can reduce colorectal cancer mortality by 15-20% but it is neither a sensitive nor specific test[48;51;162].

It has also been reported that a single flexible sigmoidoscopy screening test (and the associated relevant treatment and further investigations indicated) reduce distal colorectal cancer mortality by 60% over the next 10 years and incidence by 44% over the next 6 years[54]. However, there is chance of missing 25% of advanced neoplasia (adenomas over 1cm, villous architecture over a third of the surface, high grade dysplasia and carcinomas) in the proximal colon in asymptomatic screened groups with an isolated sigmoidoscopy and faecal occult blood test only[183]. There is more clarity now on advantage of a single flexible sigmoidoscopy in the 55 to 64 year age groups. In these asymptomatic patients the randomized arm that underwent the procedure showed 33% reduction in incidence of colorectal cancer on intention to treat analysis, 43% reduction in mortality and 50% reduction in distal colorectal cancers. The median follow up period was 11.2 years[184].

Recent meta-analysis has demonstrated a relatively modest association between distal colonic adenomas and the prevalence of proximal colonic adenomas. This association is also applicable to diminutive adenomas (adenomas<5mm or less, tubular adenoma of 10mm or less, adenoma of 10mm or less and polyp of any histologic pattern less than or equal to 5mm) in distal colon. Not, however, for hyper plastic polyps in the distal colon and hence a strong recommendation for colonoscopy in the screen-detected population with distal findings. The downside of this recommendation would be a chance of missing 1.3 to 2.4% of isolated advanced proximal adenoma with a normal distal colon. This needs to be clearly explained to patients being screened with sigmoidoscopy[185].

A recent trend in the USA is for screening by colonoscopy, and clearly a normal colonoscopy reduces the future risk of colorectal cancer by 60-70%, even 10 years after the screening colonoscopy[186]. However, the same study showed a higher incidence of right-sided colon cancers in the screened population compared to the general population after 10 years, which reflects to a certain extent the different tumour biology of right-sided tumours but, more importantly, that screening colonoscopy needs to meet stringent quality standards particularly in relation to caecal intubation rates.

The UK national screening programme with faecal occult blood testing has been underway in a programmed fashion from April 2006. This is the only screening programme for colorectal cancer in the world where centralisation of resources and sponsorship by the national Department of Health has occurred. It has unfortunately had a slow and difficult start[187].

The median age for diagnosis of colorectal cancer is 72 years, so screening as currently performed in the UK will only target 42% of cancers. Furthermore, only 57% of eligible patients accept the offer of screening, and some with positive faecal occult blood tests decline further investigation[54;180]. Taken together, this means that only around one quarter of colorectal cancer patients will be identified by screening. This essentially means that the majority of colorectal cancers will continue to be diagnosed in their symptomatic phase, at least for the foreseeable future. The role of e-RP is primarily directed to the symptomatic group of patients and not the screen detected population of CRC patients.

1.6 Referral Methods

1.6.1 Before The NHS Cancer Plan (2000)

Pre-2000, no specific rule or process governed the referral of suspected cancer patients from primary care. Similarly, no specific referral criteria were clearly available to flag the high-risk patient to a specialist. This was associated with poorly coordinated patient pathways in secondary care from the point of referral, through investigation, diagnosis and treatment.

The real inequalities noted were in terms of who got cancer, and what happened to them when they did. People from deprived and less affluent backgrounds were more likely to get some types of cancer and, overall, were more likely to die from it once they had been diagnosed[11;188]. While many cancer patients received excellent treatment, services were patchy. Patients in different parts of the country received varying quality and types of treatment – the postcode lottery of care. In the early 1990s, deaths from lung cancer

among men were nearly five times higher among unskilled workers than among professional groups.

For a number of reasons, cancer patients in England often had poorer survival prospects than in other comparable European countries[189;190]. For some cancers, such as breast cancer and bowel cancer, this was partly because patients tended to have a more advanced stage of disease by the time they were treated. This might be because they were not certain when to go to their GP about possible symptoms, or because GPs, who saw relatively few cases of cancer[191], may have had difficulty identifying those at highest risk[192;193], or because of the time taken within hospitals to progress from the first appointment through diagnostic tests to treatment[138], or a combination of all of the above.

1.6.2 Calman Hine Report

This report, "A Policy Framework for Commissioning Cancer Services – A Report by The Expert Advisory Group on Cancer to the Chief Medical Officers of England and Wales" is popularly known as the Calman Hine report. This report published in April 1995 was subsequent to the formation of an expert advisory group on cancer in response to the Government white papers "Health of the nation" and "Working for patients". These identified cancer as one of the well-defined areas in health care that needed significant improvement to improve the health standards of the people of this nation. This report laid the foundation of the current, patient-directed, multidisciplinary approach to cancer diagnosis and treatment, delivered locally with high standards[194].

1.6.3 New Structure For Cancer Services

The Cancer Plan[195] sets out the first ever-comprehensive strategy to tackle the disease. It is the first time any government has drawn up a major programme of action linking prevention, diagnosis, treatment, care and research. Published in September 2000 it was, in a way, a continuation of the Calman Hine report, but with more specific targeted emphasis on each part of the patient's journey from clinical presentation onwards, and with appropriate plans for the allocation of necessary funds for each phase of care.

The plan was to allocate additional £570 million by 2003/04 to improve cancer services by developing cancer networks across the nation that would, in turn, develop strategic service delivery plans. Similarly guidelines for network workforce, education and training and facilities strategies were to underpin service delivery plans.The Cancer Plan provides a strategy for bringing together prevention, screening, diagnosis, treatment and care for cancer, and the investment needed to deliver these services in terms of improved staffing, equipment, drugs, treatments and information systems.

A principal objective is that, by 2010, 5-year cancer survival rates will compare with the best in Europe. New funding will support the Cancer Plan, and by 2006 there will be considerably more cancer specialists, radiographers, nurses and other cancer staff.

1.6.4 Established Guidelines

Royal College of Surgeons Guidelines

The Royal College of Surgeons of England, in response to a request from the Department of Health, first drafted guidelines for the diagnosis and management of colorectal cancer in 1996. This laid the framework for clinicians to provide a uniform level of care to the highest possible standard. The recommendations from the guidelines were grouped into various categories representing the patient's journey from referral by the GP to initial investigation to various phases of treatment, follow up etc.

Improving outcomes in colorectal cancer

This NHS executive document published in November 1997 is often referred to as the COG guidelines after the 'Clinical Outcomes Group', which developed it[196]. This document was aimed to guide the commissioning, planning, and development of colorectal cancer services in a way that would benefit patients in accordance with the Royal College of Surgeons Guidelines and also conform to the pillars of Calman Hine report.

Department of Health Guidelines and Scottish Guidelines

These documents pertaining to referral of patients suspected of having colorectal cancer from primary care are discussed in more detail in the next section.

1.6.5 Two-Week-Wait (TWW) Rule

The two-week-wait rule was initially released in the Government white paper, "The new NHS – Modern and Dependable". This was further re-emphasised in the NHS Cancer Plan, which essentially ensured a maximum delay of up to two weeks from GP referral to specialist appointment for a suspected cancer patient. This rule applies to all forms of malignancies. The two-week-wait rule was sequentially introduced from 1999 onwards for each cancer site.

Site of Malignancy	Onset of Two-week Rule
Breast Cancer	April1999
Lung, Leukaemia, Children's cancers	April 2000
Upper Gastrointestinal cancers Lower gastrointestinal cancers	July 2000
Gynaecological cancers Skin cancers Brain/Central Nervous System cancers	October 2000
All other cancers including Urological, Head and Neck, Sarcomas, Haematological malignancies	December 2000

Table 11 two-Week referral rules, sequential introduction to all cancer sites

Broad outlook for main cancers

All major cancers in the UK have been incorporated into the NHS Cancer Plan and measures taken to improve outcomes in terms of survival where possible.

Early recognition of symptoms and appropriate criteria for speedy referral have been formally introduced as guidelines for primary care doctors[195]. However, the speedy introduction of these major reforms has been criticised due to inadequate training and funding for primary care doctors to provide quality service for early cancer detection[56].

Colorectal Cancers

The two-week-wait rule for referral of patients with suspected colorectal cancer was primarily designed by the ACPGBI and the Royal Colleges. The main criteria to refer patients as TWW are mentioned in table 12 and exclusion criteria in table 13.

• Rectal bleeding WITH a change in bowel habit to looser stools and/or increased frequency of defecation persistent for 6 weeks at all ages.
• Rectal bleeding persistently without anal symptoms (such as soreness, discomfort, itching, lumps or prolapse) in patients over 60 years*.
• Change of bowel habit to looser stools and/or increased frequency of defecation, without rectal bleeding and persistent for 6 weeks.
• A definite palpable right-sided abdominal mass.
• A definite palpable rectal mass.
• Iron-deficiency anaemia without an obvious cause.

Table 12 TWW criteria for suspected colorectal cancer referrals

Rectal bleeding with anal symptoms.
Change in bowel habit to decreased frequency of defecation and harder stools.
Abdominal pain without clear evidence of intestinal obstruction.

Table 13 Criteria excluded from the TWW rule

Yield of the Two-Week-Wait referral system

Various studies/audits have shown the yield of CRC through the TWW system to vary between 2 and 22% and the CRC referred through the TWW comprised between 0 and 47%[197], but a systematic review of 12 relevant studies quotes a yield of 10.3% of CRC through the TWW referral system and only 24% of CRC referred as TWW[198]

Misuse of the Two-Week-Wait referral system

A study from Portsmouth colorectal unit has demonstrated noncompliance from GPs in using the TWW system[62]. This was most often seen in patients with rectal bleeding where presence of anal symptoms was not accounted for and who were incorrectly sent as TWW. Right-sided abdominal mass and palpable rectal mass were other criteria predominantly used wrongly. This has been partly shown to be due to lack of awareness of referral criteria, i.e. a gap in the education of the GPs[192].

1.7 Delays in the Treatment of Colorectal Cancer

Multiple factors could influence the pathway of patients with colorectal cancers from onset of first symptom to start of definitive treatment. The whole process from the patient being aware of symptoms, deciding to attend a doctor and the subsequent chain of events are linked with time periods that would potentially slow the diagnostic and treatment process.

It is of utmost importance to reduce delay in patient pathways with suspected CRC. The psychological morbidity is considerable in patients with delay in referral and treatment, especially if the disease is incurable. It is important that this issue is addressed by developing clear strategies in relation to patient presentation to GP, referral by GP to secondary care and the subsequent pathways in secondary care.

1.7.1 Patient Factors

Patients maybe ignorant of the significance of symptoms or reluctant to report the symptoms to their General Practitioner[199;200]. A mailed questionnaire study involving over 18000 participants showed that there were misperceptions about the risk factors leading to CRC in the population studied [200].

<u>Ignorance of presenting symptoms</u>

Lack of awareness

An interview-based survey done on 1637 people showed clearly that 58% of respondents could not list any colorectal cancer risk factors and 24% were not able to mention any warning signs of cancer. This study also highlighted that low knowledge was associated with negative attitudes and lower intentions to participate in a screening process[201]. Sundaram et al reported, out of 1633 patients, a figure of 12% and 9% respectively who never examined their stools or toilet paper. This could potentially delay the presentation of colorectal cancer in this group of people[202].

Poor educational and socio-economic status and higher stress levels are also considered contributory factors in lack of awareness.

<u>Inertia and lack of insight in reporting symptoms</u>

Studies have shown that some patients, in spite of noticing symptoms like rectal bleeding, fail to report to their doctor. Perception of the seriousness of the symptom has been found to be the most important factor in deciding whether to consult a doctor for rectal bleeding[92]. Those over 60 and those noticing blood mixed with stool were most likely to consult a doctor[92].

American and European studies have shown that beliefs about health and concerns about symptoms are more important determining factors for consulting a doctor than severity and frequency of symptoms[203]. Similarly, belief of cancer risk will also influence screening rates[204]. Public awareness campaigns are a possible method of educating the general population about CRC, in addition to the formation of organisations addressing these issues at the local level[205].

Fear of doctors and investigations

Sometimes fear plays an important role in patients deciding against medical consultation, and this can result in delayed presentation at a worsening stage of the disease.

Fitness of patient referred

Elderly, infirm and housebound patients are unlikely to recognise relevant symptoms or to take the initiative to be seen by GPs and have them investigated. This in itself could cause delays, which, however, might not alter the overall management of these patients.

1.7.2 General Practitioner Factors

Delay by the GP is well illustrated in the paper by Holliday and Hardcastle[206], where only one third of patients with symptomatic disease were referred to secondary care at the first GP visit. Half the patients had been seen three or more times by GP before being referred. In a recent paper, over 50% of cancer patients who met the referral criteria had not been referred through the fast track system[62].

Over-investigation may have physical or psychological ill effects on patients as well as having implications for cost and resources. The safe use of 'watchful waiting' needs considerable clinical skill to avoid excessive delays in referral of patients with cancer, particularly if presenting with low-risk CRC symptoms[109]. The unnecessary worry and fear of cancer created in individuals with a low risk and the potential for complications from investigations would deter most GPs from sending patients via the fast track route.

This has been demonstrated in a recent study looking into the 'false positive' category of screened patients awaiting a diagnostic workup. They mainly expressed emotional symptoms including anxiety and fear of death, but in addition some were concerned about physical symptoms in relation to the diagnostic tests[207]. This approach requires both patient and doctor to have confidence in the decision made. However, this has also contributed significantly to delays in referral, and delays from referral to diagnosis and treatment initiation in secondary care.

Compliance with guidelines

The guidelines for referral of patients suspected to have CRC have been in place since 2000. However, there have been a number of studies and audits showing non-compliance of GPs in using the guidelines appropriately, contributing to the low yield of CRC from the TWW referral system[109;208;209].

Inappropriate clinical evaluation

This has been recognised as eliciting both colorectal symptoms and signs. There was evidence of over 72% discrepancy between the GPs' clinical finding of an abdominal mass compared to that of the hospital doctors[62]. Summerton in his paper also indirectly quotes figures of inappropriate or no clinical evaluation in those who had been referred for barium enemas to rule out CRC[210].

Appropriateness of referral urgency

It is well known that GPs often fail to refer patients appropriately through the TWW rule and often over 50% of CRCs diagnosed in secondary care come via the routine route[62]. This has also been demonstrated in my validation study where only 43% of CRC patients were referred as TWW[138].

Appropriateness of referral destination

This has been more recently looked into by many service providers and probably is equally relevant in accounting for delays in diagnosis.

Patients often are referred to the wrong specialty for inappropriate tests and multiple secondary care episodes before definitive diagnoses. These factors are thought to be predominantly due to lack of awareness by the referring GPs[138;170].

1.8 Initiatives To Improve Colorectal Cancer Care Standards And Outcomes

The Department of Health, along with the Royal Colleges, has introduced various measures since 2000 to improve CRC patients' care and outcomes – the setting up of a TWW referral clinic, the colorectal cancer referral guidelines, the setting up of a robust multidisciplinary team (MDT) in any hospital dealing with these patients, cancer specialist nurses and nurse endoscopy clinics, to mention a few[150;195-197;205;211-213].

Hopefully, the colorectal cancer screening programme, rolled out since 2006, will result in earlier detection and possibly down-staging in the long run[48;49;214].

The Cancer Services Collaborative

The Cancer Services Collaborative is a national initiative to improve the expertise and outcomes of care for patients with suspected or diagnosed cancer by optimising systems of care delivery. Nine cancer networks took part in the first phase of the programme that commenced in September 1999.The second phase of the programme in April 2001 included every cancer network in the NHS.

The Cancer Services Collaborative has shown that delays in getting treatment for people with cancer are often caused by the way that the system for delivering care is organised. By redesigning the system, significant improvements can be made. Teams within the nine networks taking part in the Cancer Services Collaborative are still continuing to redesign services for patients with suspected and diagnosed breast, bowel, lung, ovarian and prostate cancer.

Many of the projects have been able to demonstrate reductions in time-to-diagnosis and/or time-to-treatment of weeks or even months. A major emphasis of the Cancer Services Collaborative is on redesigning services from the patient perspective, building skills for improvement, and on multidisciplinary teams working together to diagnose problems and make effective and sustainable changes.

1.9 Decision Support

The concept of using decision support in primary care has primarily evolved in the last two decades[215]. There have been a varied number of decision support tools implemented, mainly for medical conditions[216;217], carrying out blood tests[218] and treatment guidelines[219]. Introduction of these technology-based adjuncts in clinical care often have significant barriers on both the logistics side of things and with individual clinicians and staff in primary care[220-222]. However, interestingly, one study quotes that the age of the GP is not a bar in their use of decision support or online guidelines[221]. There has been very supportive data to encourage increased use of decision support systems especially in the case of primary care doctors[221;222] and those practicing in rural parts[223]; training issues, however, have always been cited as a major factor to improve usage[224].

Ebell et al. in their paper mention GPs' preferences in the use of decision support include having it on handheld computers and networked desktops, being updated regularly, having an overview of treatment guidelines and being alerted to adverse reactions to drugs while prescribing[225].

Though earlier studies have been dubious as to the benefits of decision support in primary care, a recent paper looking at a one-stop breast clinic assessing the need for triple

assessments, strongly supported the use of a decision support tool which resulted in statistically significant reduction in errors (60 out of 120 errors without decision support to 16 out of 120 errors with decision support)[226].

2 Inter-General Practice Variability In The Use Of Colorectal Referral Guidelines

2.1 Introduction And Methods

The colorectal cancer referral guidelines and TWW (Two-Week-Wait) clinics for suspected colorectal cancer were introduced in July 2000[227;228]. However, this pathway for referral to secondary care has been shown to be often used inappropriately[62;79;193;209;229;230]. There have been suggestions that this reflects poor referral guidelines[79;193] and/or their inappropriate use by General Practitioners (GPs)[109;209].

This prompted me to get more information about the referral of patients with suspected CRC to a single secondary care center – Royal Bournemouth hospital – from the local general practices that traditionally use it.

I aimed to assess the pattern of referral behind the current low yield of colorectal cancer from the TWW referral system. The influence of other factors including General Practitioner age, educational input and population demographics were also explored.

Methods for the study

Each General Practitioner (GP) has a unique code and each general practice is coded as well. The referrals received from primary care can be traced to the General Practitioner and the general practice through these codes.

From a prospectively recorded database of all colorectal cancer patients, data extraction for a period of one year from April 2004 to March 2005 linking GP codes against each colorectal cancer patient diagnosed was carried out.

Further data was extracted, assessing the number of TWW referrals made in the same time period, linked to GP codes. The total number of colorectal cancers, the route of referral and the number of TWW referrals were then analysed for each GP code and also individual general practices.

Forty-nine general practices within four Primary Care Trusts (PCTs) were involved in the study. These general practices were selected based on the previous years' (2001 to 2004) data on colorectal cancer patients. Consistent referral of CRC to this secondary care hospital was used as the principle criteria to include the general practices. This resulted

in 5 general practices being totally excluded as they partly referred their patients to Poole hospital.
To ensure further accuracy, the 49 general practices included were contacted to verify their referral practice, i.e. that colorectal and gastroenterology referrals were to Royal Bournemouth Hospital.

Primary Care Trusts provided data on the population of each general practice and the subgroup of patients aged 60 years and above. The educational needs of GPs and their awareness of colorectal referral guidelines were assessed by an anonymous postal survey.

To test factors that could account for variability, I analysed the ages of the General Practitioners, the age characteristics for each practice population and their influence on referral patterns. Socio-economic indicators were not analysed due to lack of accurate indicators at practice population level and information only being available at "Lower Layer Super Output Area" (Information from Office of National Statistics).

Statistics

The CRC ('total' and 'CRC as TWW') were derived per 1000 general practice population and 95% confidence intervals calculated.

Similarly the TWW referrals were compared per 1000 general practice population for all the 49 general practices. The percentage of each practice population 60 years or above was derived.

The Statistical Programme for Social Sciences (SPSS v12) was used for analysis. A value of $p<0.05$ was considered significant.

2.2 Results

There were 189 patients with colorectal cancer diagnosed in the twelve-month period of the study. Of the 189 patients, 175 were referred to secondary care directly by GPs and this forms the basis of further analysis.

Fourteen patients were not included, as eleven were referred privately and three were internal referrals from other departments. The colorectal unit received 537 TWW referrals in this time period and all except three had identifiable GP codes. These 175 patients with colorectal cancer, and 534 TWW referrals for patients with suspected colorectal cancer, originated from 202 GPs in 49 general practices spread over four PCTs, referring to the Royal Bournemouth Hospital.

Of the 175 patients with colorectal cancer, 121 were outpatient referrals and 54 were referred as emergencies. Of the 121 outpatient referrals, 60 were referred as TWW, 43 as urgent and 18 as routine referrals. The urgent and routine colorectal cancer patients (n=61) were diagnosed from 3397 referrals to colorectal and gastroenterology clinics.

Analysing these patients, we found marked variability in the use of the TWW referral pathway (Figure 5). The median number of TWW referrals per general practice was 8 (range 0-47).

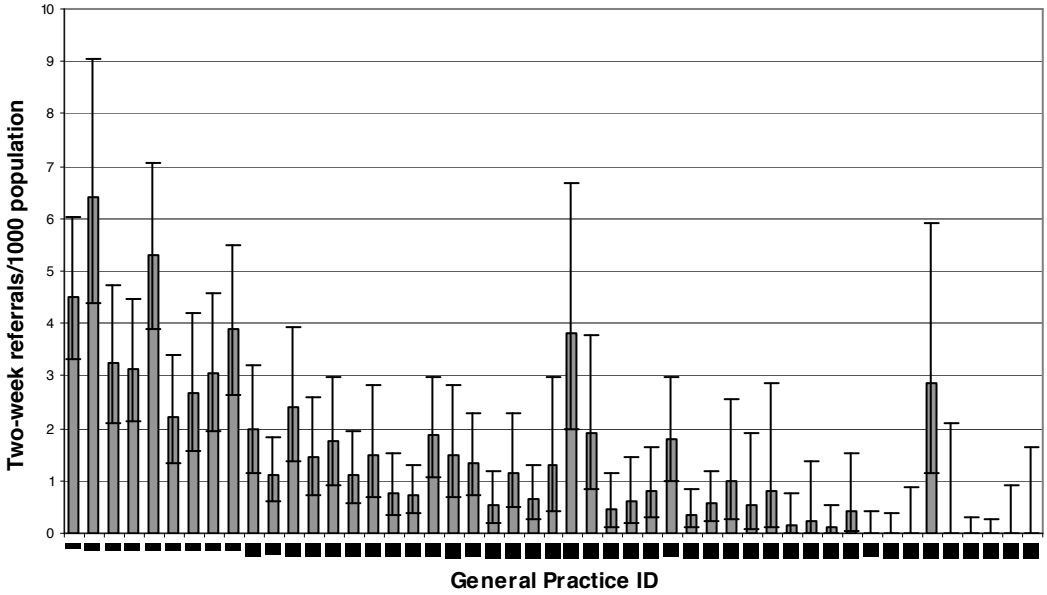


Figure 5 Variability in numbers of TWW referrals from 49 general practices per 1000 practice population. Bars represent 95% confidence intervals. Median number of TWW referrals per general practice was 8 (range 0-47).

A wide variation in the yield of colorectal cancer from the 49 general practices was observed. The median number of patients with colorectal cancer referred by each general practice was 3 (range 0-10). Figure 6 depicts the number of patients with colorectal cancer per general practice (all routes) and colorectal cancer diagnosed as TWW referral per general practice.

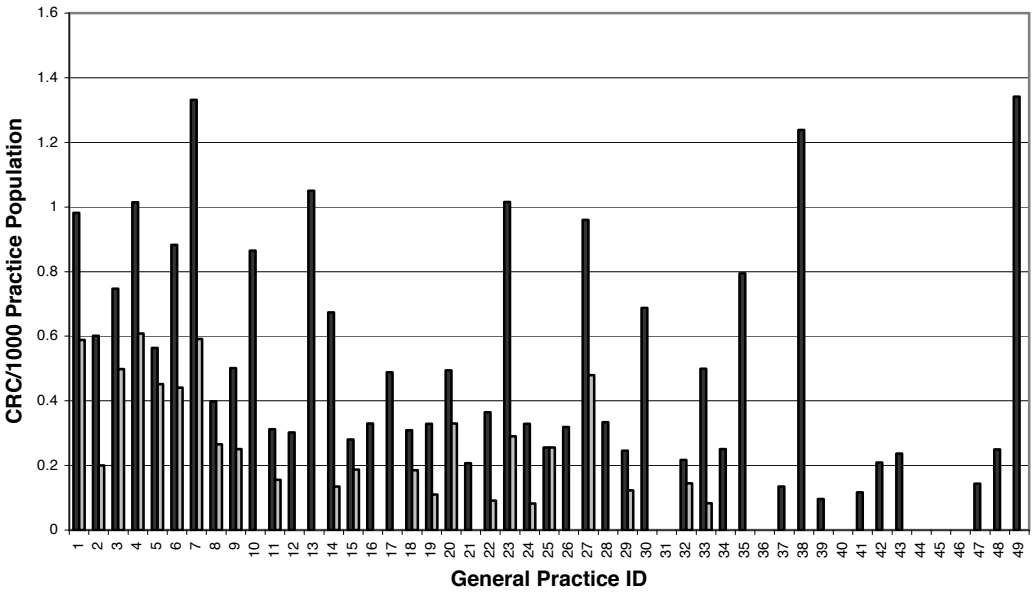


Figure 6 Variability in numbers of colorectal cancers referred from 49 general practices per 1000 practice population. Black - Total colorectal cancers (all routes), Grey- TWW referral diagnosed to have colorectal cancers. General Practice ID numbers correspond to those in chart 1. Confidence intervals omitted for clarity of graph. Median number of colorectal cancers referred per practice was 3 (range 0-10).

Among general practices, the median population aged 60 years and above was 28% (range 11.2% to 53%) and there was no statistical correlation of age with the yield of colorectal cancers per practice (p=0.79; Spearman correlation coefficient r_s= -.038, two-tailed).

Median age of GPs in this study was 47 years (range 32 to 63). A positive correlation was noted between increasing age of GP and the total number of patients referred with colorectal cancer through all routes (p=0.002, Spearman correlation coefficient, r_s=. 236). No significant association was noted between GP age and either number of TWW referrals made (p=0.639) or colorectal cancers diagnosed as TWW (p= 0.34).

There was a significant tendency towards a higher number of TWW referrals from practices with a higher incidence of colorectal cancer (p=0.001; Spearman correlation coefficient r_s = 0.447, two-tailed). This is depicted in the scatter plot (figure 7). This plot also shows two types of scatters. Firstly, general practices with a higher number of TWW referrals and very few colorectal cancers diagnosed, and secondly general practices with little or no use of the TWW referral pathway and colorectal cancers being referred through other routes.

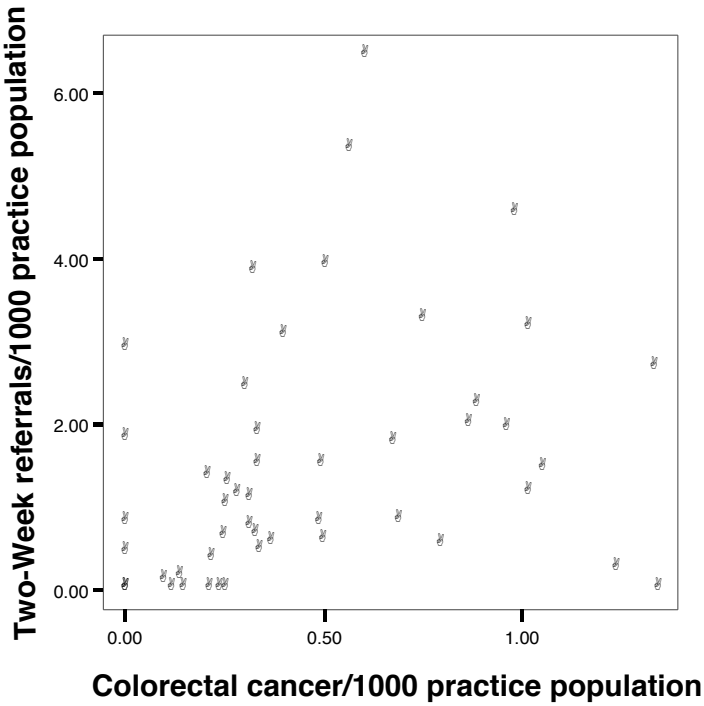


Figure 7 The scatter plot of TWW referrals per 1000 practice population vs. colorectal cancers per 1000 population per general practice. There was a significant tendency towards a higher number of TWW referrals from practices with a higher incidence of colorectal cancer. (p=0.001; Spearman correlation coefficient r_s = 0.447, two-tailed)

Twenty-six of 49 (53%) general practices had no colorectal cancers diagnosed via the TWW referral route, during the 12 months of this study. These practices had significantly lower utilisation of the TWW referral pathway compared to the other 23 practices (p=0.002, Independent samples t-test, CI of difference of mean 0.51-2.08) (Figure 8).

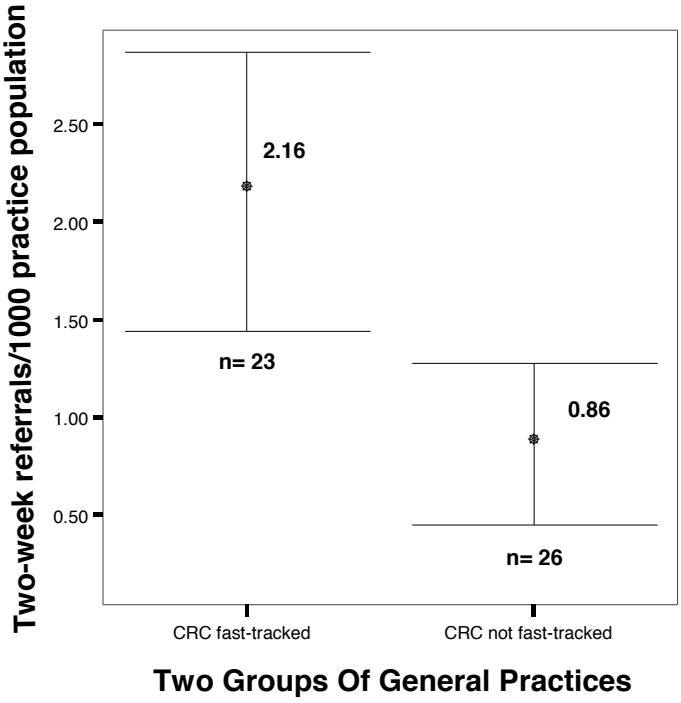


Figure 8 Numbers of TWW referrals per 1000 population for those practices who referred a CRC as two-week-wait referral during the study period and those practices that did not. Bars represent 95% confidence intervals. Practices that did not have any CRC diagnosed via the TWW referral route during the 12-months of this study had significantly lower utilisation of the TWW referral pathway (p=0.002, Independent samples t-test, CI of difference of mean 0.51-2.08)

The postal survey GPs had a 57% response rate (129/228). One hundred and one GPs (78%) claimed to be aware of colorectal cancer guidelines. However, only 8% of General Practitioners answered correctly to the question *"How many fast-track criteria exist?"* Ninety-one GPs (71%) mentioned that they had not received any training on colorectal referral guidelines and 70 GPs (55%) expressed a wish for this to be rectified. Only 34 GPs (26%) had received either formal or informal training, of which 31 GPs (91%) said that training had been in the last two years. None had received any training sessions at the implementation of the guidelines in July 2000.

The decision to use the TWW referral route by GPs was influenced primarily by "specific red flag signs" in 85%, clinical concern in 74%, symptom clusters in 61% and guidelines in 58%. Only 9% and 12% of GPs mentioned fear of litigation and patient pressure as influencing their decision to refer patients as TWW. (See table 14 for detailed survey results)

	Survey Questions	Number of GPs		Percentage	
1	Are you aware of Colorectal Cancer Fast-Track referral guidelines?				
	Yes	101		78.3	
	No	13		10.1	
	Not sure	15		11.7	
2	How many fast-track criteria exist?				
	Four	18		14	
	Five	10		7.8	
	Six	10		7.8	
	Seven	6		4.7	
	Not sure	85		66	
3	Have you received any training in use of colorectal referral guidelines?				
	Yes (formal)	17		13.2	
	No	91		70.5	
	Yes (Informal)	17		13.2	
	Not sure	4		3.1	
4	If **Yes,** when?				
	Within last 2 years	31		91.2	
	3-4 years ago	3		8.8	
	5-6 years ago	0		0	
5	Would you be interested in an education session?				
	Yes	70		55.1	
	No	31		24.4	
	Not sure	26		20.5	
6	What influences your decision to use fast-track referral route?	Yes	No	Yes	No
	Guidelines	75	54	58%	42%
	Cluster of symptoms	78	51	60%	40%
	"Red Flag" signs	109	20	84.5%	15.5%
	Patient Pressure	15	114	11.6%	88.4%
	Clinical concern	95	34	73.6%	26.4%
	All of the above	18	111	14%	86%
	Fear of litigation	11	118	8.5%	91.5%

Table 14 Results of the postal survey (n=129)

2.3 Discussion

The current Department of Health guidelines for suspected colorectal cancer were designed to be used by GPs in primary care as a guideline to prioritise referral. These referral guidelines may have helped to improve awareness of significant symptoms and to have formalised referral pathways. A modest reduction in the emergency presentation of colorectal cancer since 2000 has been noted in a few centres [231]. However, a recent paper has mentioned a reduction of 12% in emergency presentation of colorectal cancer and fewer Duke's D disease at presentation after the introduction of TWW clinics[232].

Several studies have cited pitfalls in the referral guidelines and highlighted concerns that this might lead to poor yields [79;209], as the guidelines lack sensitivity and specificity. Weighted numerical scores and patient questionnaires have been assessed, to try and improve the yield of colorectal cancer, without overloading the referral system[79;233].

However, this does not address the variability noticed among general practices in utilising the existing TWW referral pathway, as demonstrated in this chapter. The postal survey highlights the knowledge and education gap within primary care in relation to TWW referral, and we can speculate that these factors in part explain the variability in referral practice.

Increasing age of GPs in this study was associated with increased referral of colorectal cancers to secondary care. This is difficult to explain given the move to unified lists in primary care, but it may be a manifestation of patient preference (older patients preferring senior GP partners). Alternatively, it may simply be a chance finding, as the actual number of colorectal cancers from each general practice was small. There was, however, no significant association between the age of GPs and colorectal cancers diagnosed through the TWW route or the number of two-week-wait referrals made. This finding is at variance with a large Finnish study looking at all referrals to secondary care. The significant determinants for reduced referral were increased clinical experience in male doctors and attendance at continuous medical education programmes. Young GPs, locum doctors and female doctors tended to refer more to secondary care[234].

Subsequent to our study, I fed back the data on variability to individual GPs, including their position in figure 6 with a unique identifier to enable comparison with the other 48 practices on an anonymous basis. Also in response to the survey, targeted educational sessions have been held in 20 practices to date. Since a full-time GP sees roughly one colorectal cancer per year or one colorectal cancer patient in 1800 practice population[191], it is vital the GPs have appropriate awareness of referral criteria for the TWW referral system to work efficiently.

Utilisation of GP and general practice codes may be a useful audit tool to improve referral practices from primary care. This method can be employed to analyse GPs' referral practices, and may be a useful method of self-assessment, addressing the issue of inappropriate referrals from individual practices or primary care cancer networks. The method employed in this study can be used to identify outlying general practices and target education as appropriate.

This study suggests that the guidelines can be used more effectively, and I believe that the current guidelines have not been given the opportunity to work.
Whilst this study supports the use of a specific TWW referral pathway for suspected colorectal cancer, it also highlights the fact that, in many general practices, there is little or no utilisation of this pathway. General Practitioner education is needed to improve implementation of the existing referral guidelines.

3 Main Study-Introduction

The rationale for the study was born out of need for streamlining referral mechanisms from primary care, not only for suspected colorectal cancer referrals but also to process patients with lower gastrointestinal symptoms and suspected iron deficiency anaemia patients adequately.

This has relevance since the two-week referral system has attempted to streamline suspected colorectal cancer referrals, though with consistently poor yields varying from as low as 3% to 20% in various cancer networks in the country. This essentially forces the resources in secondary care to cater to the other 80-97% of referrals that have a normal or benign pathology, but need investigation on a two-week basis. Only a handful of NHS providers had received extra funding to cater to these needs at the time of the introduction of these rules in July 2000, and most centres required reorganisation of existing services. This has left a large group of patients disadvantaged with possible high or low-risk symptom clusters for colorectal cancer who will, in the majority of cases, still require full colonic imaging in order to rule out malignancy and offer reassurance.

On symptoms alone, it is often impossible to discriminate accurately between malignancy, other GI conditions (diverticulitis, polyps, inflammatory bowel disease, etc) and even normal outcomes. These large cohorts of patients coming from primary care as routine referrals have over 50% of the colorectal cancers being referred to secondary care in a year. The potential difficulties with the two-week-wait rule have been demonstrated in various studies, and measures to circumvent it have been tried[62;208;209;229;235-239]. Awareness of colorectal cancer guidelines have been extremely variable among general practices and even within the same general practice[192](Chapter 2). This has substantially affected the yields from the two-week wait pathway and thus also potentially disadvantaged CRC and other significant benign pathology coming as routine referrals.

Current Practices

There is limited guidance on how to decide which patients need investigations and which do not. Similarly there is no clear guidance in primary care on where a patient with various colorectal symptoms should be seen in secondary care – outpatient clinic, flexible sigmoidoscopy, colonoscopy, barium enema, and CT colonography, combined gastroscopy or colonoscopy for suspected iron deficiency anaemia.

There is no published scientific evidence to suggest which of these strategies may be preferable, especially when referred by General Practitioners, though a group in Leicester have tried a protocol-based referral for Department of Health high-risk symptoms[170;240]. The evidence supporting the use of one strategy over the other is anecdotal at best and

usually based on the personal preferences of the clinician involved and the availability of resources. Valuable resources in secondary care need to be used efficiently to investigate and treat patients with colorectal symptoms and/or suspected anaemia. The concept of straight to test has relevance in placing patients in appropriate investigation pathways as first consultation in secondary care, based on the probabilities of possible pathology and the location of the same in the colon or rectum. Artificial neural networks have been developed in one tertiary centre to assess the need for colonoscopy in accurately predicting the presence of pathology in patients attending routine outpatient appointments with over 90% sensitivity and specificity[241]. These instruments have to be tried in the general population to work out the applicability and utility of the tool.

The Possible Way Forward

A validated protocol for referral of patients addressing the full spectrum of lower gastrointestinal symptoms and suspected or proven iron deficiency anaemia would likely help the General Practitioners. This would hopefully streamline referrals to appropriate clinics with appropriate urgency assigned so that we don't disadvantage patients with colorectal cancer who have been diagnosed via the routine route. It would also streamline referrals to identify significant benign conditions that need more urgent investigations in secondary care. The incorporation of this referral protocol in the GPs' day-to-day referral mechanism would prompt consistent usage of it.

3.1 Development Of Lower GI e-Referral Protocol (e-RP)

The mapping of patient pathways from point of referral to diagnostic work up in secondary care was done subsequent to a combined discussion of relevant clinical pathways with gastroenterologists, the staff of the radiology department and a colorectal surgical team. The pathways developed were also based on existing current literature of high-risk symptoms and signs and their clusters described in both primary care and secondary care studies for colorectal cancer[50;78;79;82;83;88;89;107;109;141;143] .

3.2 Opportunity With Choose And Book

The introduction of the 'National Programme for Information Technology' (NPfIT) has given patients the option to choose up to four or five service providers (secondary care or tertiary care centres) for their ailment. This has been a revolutionary concept, with promises of a national spine holding all patient details electronically to be accessed in secondary or primary care with the press of a button [242].

While the expected deadlines for national implementation of such a large project had significant delays, as would be anticipated, in some areas the targets and pilot runs were done much earlier. This secondary care centre with the referring PCTs had taken

measures to meet early deadlines and was one of the very few areas achieving national targets with respect to usage of Choose and Book by GPs (fig 9).

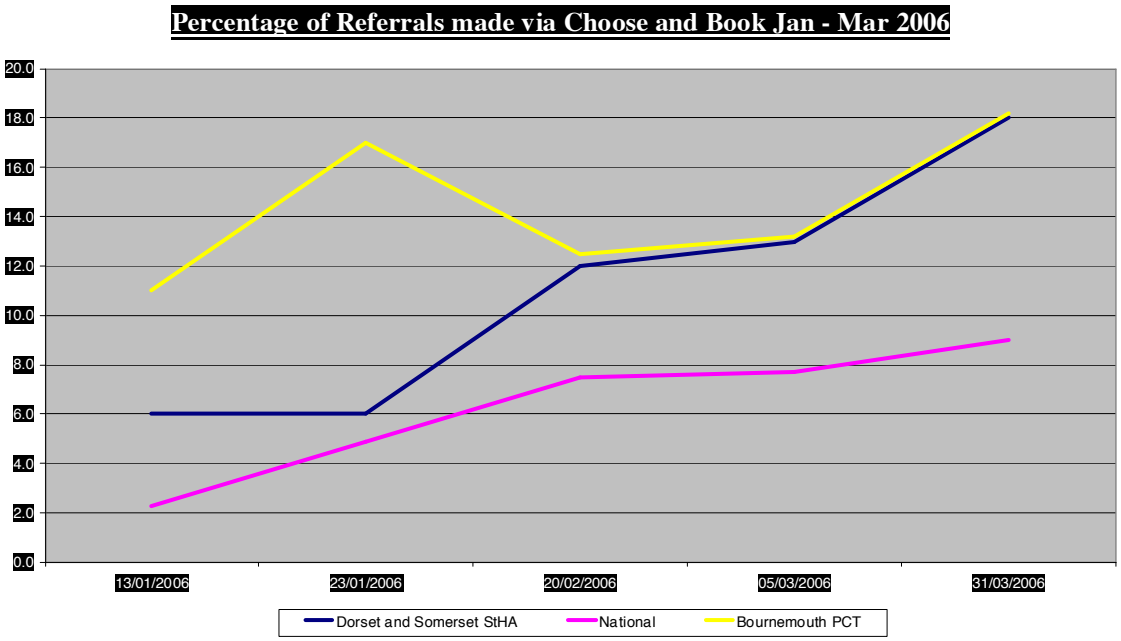


Figure 9 The comparison of use of 'Choose and Book' in local PCTs with national figures and local SHA figures

However, this new referral method was associated with significant glitches, both software and hardware-based. While they were being addressed, the initial resistance to using the Choose and Book gave way to increased usage by most GPs towards the end of 2005. Multiple clinics with different names assigned by various service providers (secondary and tertiary hospitals) would be seen on the screen of the GP's computer. It is a difficult and time-consuming task to book a patient correctly to an appropriate clinic during the short consultation episode with the patient.

Often this work is left to be done by the GP towards the end of the day's consultations and/or to be done by clerical staff with little knowledge of the patient's symptoms and appropriateness of referral. Moreover, in spite of TWW rules for suspected cancers, over 50 % of colorectal cancers and other serious lower GI pathology are referred as routine.

This gave us an opportunity of introducing a decision support system into the Choose and Book software programme. We linked the outcome page of decision support to the clinic appointment page directly (straight to test when needed) as well as the self-grading of referrals with the option for GPs to override the decision support with respect to the referral urgency or destination assigned by the e-RP.

4 Methods

The methods section begins with the validation study of the e-RP. Methods sections for the main study follow this

4.1 Validation Study of The e-RP

This was a three-armed validation study done using data over three time periods; namely one hundred consecutive colorectal cancer patients treated in the 2002-2003 time period, one hundred two-week referrals collected prospectively in 2004-2005 and one hundred routine referrals from the 2002-2003 period. The reason for the earlier time period for cancer patients and routine referrals was the delay to diagnosis and treatment, and to allow data on process, patient pathways and outcomes to be gathered. The symptoms from the referral letter and secondary care clinical consultations were recorded onto a database and subsequently processed through e-RP. The e-RP was designed on the basis of the higher predictive power given to high-risk symptoms and combinations of symptoms and signs for CRC, while processing other lower-risk symptoms appropriately in a pragmatic fashion.

Importantly the e-RP was evaluated not only on its ability to deal with CRC, but the whole lower gastro-intestinal referral profile, incorporating medical gastroenterology, colorectal surgery and everything from CRC, through colitis and irritable bowel to haemorrhoids, fissures and rare conditions such as anal cancer. In addition, we assessed the e-RP intelligence on two important aspects. Firstly assigning the correct degree of urgency {Two-Week-Wait [TWW], Urgent, and Routine} and its ability to upgrade or downgrade effectively. Secondly, assigning the correct destination in secondary care, i.e. Straight to Test (rigid sigmoidoscopy, flexible sigmoidoscopy, colonoscopy, combined gastroscopy and colonoscopy for suspected iron deficiency anaemia, barium enema) and appropriate speciality (medical, surgical).

The Lower GI e-Referral protocol was revised based on initial validation results, the 300 referral episodes were rerun to maximise sensitivity, the actual delays patients experienced were calculated from date of referral to date of definitive treatment and the number of hospital episodes prior to start of treatment for colorectal cancer was assessed. Statistical analysis was done using SPSS v.12 and a 5% level of significance assigned.

Location Of Cancer	Frequency	Percent
Caecum	18	18.0
Ascending colon	4	4.0
Hepatic flexure	2	2.0
Transverse colon	5	5.0
Splenic flexure	5	5.0
Descending colon	4	4
Sigmoid colon	22	22.0
Rectum	31	31.0
Synchronous	1	1.0
Polyp	8	8.0
Total	100	100.0

Table 15 Distribution of colorectal cancer by site in arm 1 of the study

4.1.1 Retrospective Colorectal Cancer Arm

One hundred colorectal cancers patients were analysed in the first arm of the study. Rectal (31%), sigmoid (22%) and caecal carcinomas (18%) predominated in the series (Table 15).

Only 1 out of 18 patients with caecal cancer and 1 out of 5 patients with a transverse colon tumour had colonoscopy as the first point of contact in secondary care. In contrast, the e-RP assigned 9 out of 18 patients with caecal cancers and 3 out of 5 patients with transverse colon cancers to colonoscopy as a first point of contact in secondary care via TWW (Table 16). Five patients with caecal cancers had a suspicious mass in the right iliac fossa and were appropriately directed to the colorectal surgery outpatient clinic as TWW by the e-RP. Two caecal cancer patients with signs of obstruction were directed to Accident and Emergency by the e-RP. Only one patient was directed for a routine colonoscopy and one for a two-week-wait flexible sigmoidoscopy. The detailed analysis of the pathways (actual, e-RP and e-RP revised) has been depicted based on cancer location in table 16.

Cancer Location	Actual Urgency	e-RP Urgency	Revised e-RP Urgency	No. of Actual Appointments to definitive treatment (range)	Actual median time referral to treatment in days (Range)
Caecal (n=18)	7 TWW *(1C'Scopy, 1 FS 5 OPD)* 4 A&E 3 Urgent OPD 4 Routine OPD	12 TWW *(6 C'Scopy, 5 OPD 1 FS)* 2 A&E; 3Urgent C'Scopy; 1 Routine OPD	15 TWW *(5OPD, 9C'Scopy, 1FS)* 2 A&E; 1Routine C'Scopy	3 (0-5)	33 (2-82)
Ascending (n=4)	2 A&E 2 Routine OPD	3 TWW *(1C'Scopy, 1OPD 1 FS)* 1 A&E	3 TWW *(1C'Scopy,1 OPD 1 FS)* 1 A&E	2 (0-3)	8 (1-124)
Hepatic flexure (n=2)	2 A&E	2A&E	2A&E	0, 1	1 (0, 2)
Transverse (n=5)	2 TWW *(1C'Scopy, 1 OPD)* 1 A&E 1Urgent FS 1 Not known	4 TWW *(3 C'Scopy, 1 FS)* 1 A&E	4 TWW *(3 C'Scopy, 1 FS)* 1 A&E	3 (0-7)	51 (4-58)
Splenic Flexure (n=5)	1 A&E 2 Urgent FS 1 Urgent C'Scopy 1Urgent OPD	4 TWW *(3FS, 1C'Scopy)* 1Routine C'Scopy	4 TWW *(3FS, 1 C'Scopy)* 1Routine C'Scopy	3 (1-4)	59 (37-124)
Descending (n=4)	1TWW (OPD) 2 Routine OPD 1A&E	3 TWW *(1FS, 1C'scopy, 1OPD);* 1 A/E	2TWW *(1C'Scopy,1OPD)* 1 Urgent FS, 1 A&E	4 (0-5)	39 (4-93)
Sigmoid (n=22)	13 TWW *(9 OPD, 4 FS)* 4 Urgent *(1 OPD, 2 FS, 1 C'Scopy)* 2 Routine OPD 3 A&E	11TWW *(7 OPD, 4 FS);* 5 Urgent C'Scopy; 2 Routine; 2 A&E; 2 Other	20 TWW *(6 FS, 7 C'Scopy, 7 OPD);* 2 A&E	4 (0-7)	56 (0-160)
Rectum (n=31)	15 TWW *(9 FS, 6 OPD);* 2 A&E 6 Routine OPD 8Urgent *(1C'Scopy, 2OPD, 5FS)*	23 TWW *(15 FS, 8OPD)* 7 Urgent C'Scopy 1 Routine FS	30 TWW *(15 FS, 8OPD,7 C'Scopy);* 1 Routine FS	4 (0-7)	56 (16-149)

Malignant Polyps (n=8; Rectum5, Sigmoid2, Left colon 1)	5 TWW *(5FS)*, 2Urgent (1FS, 1OPD) 1Routine OPD	6 TWW *(5FS, 1OPD)*, 2 Routine FS	6 TWW *(5FS, 1OPD)*, 2 Routine FS	2 (0-5)	58 (10-486).
Synchronous Tumour (Sigmoid and Caecum) (n=1)	1 Routine OPD	1TWW *(C'Scopy)*	1TWW *(C'Scopy)*	4	106

Table 16 The detailed analysis of actual and e-RP assigned urgency and destination for 100 consecutive colorectal cancers. TWW = Two week wait appointment; OPD = Outpatient Department; C'Scopy = Colonoscopy; FS = Flexible Sigmoidoscopy; A&E = Accident and Emergency. Delay refers to time period between referral and start of definitive treatment.

Analysing patients with left-sided tumours (distal to splenic flexure n=57) the cancers were detected in 39 patients (68%) by flexible sigmoidoscopy, outpatient rigid sigmoidoscopy and/or as a mass palpable abdominally or rectally using the revised e-RP (Table 17). While 22 colorectal cancer patients with left-sided tumours were referred as non two-week-wait referrals, the e-RP successfully upgraded 20 out of 22 to TWW status (excluding referrals to A&E).

	FS (TWW)	***Other (TWW)***	***Urgent Colonoscopy***	***Urgent FS***	***Urgent OPD***	***A&E***	***Routine***
Actual Route	13	16	2	7	3	6	10
e-RP (Revised)	21	31	0	1	0	3	1

Table 17 Comparison of first port of consultation in secondary care for left sided tumours (n=57). Actual route to revised e-RP compared. TWW: Two-Week Wait appointments; OPD-Out Patient Department appointments; FS: Flexible sigmoidoscopy. Other (TWW): -Colonoscopy and Outpatient appointments as two-week-wait.

As regards actual pathways, 43% of patients with CRC were treated as TWW referrals, but the original e-RP successfully identified 67% of patients with CRC as TWW referrals (Pearson Chi square=5.74, 1 d.f; p=0.017). This included 8 of the 18 patients who actually

presented via a delayed route (Routine and Internal). Combining the patients with colorectal cancer referred as TWW referrals and urgent referrals (patients seen within 4 weeks of referral), 82% patients with CRC would have been seen within 4 weeks of referral using the e-RP (Pearson Chi square=14.44, 1d.f;p<0.001). e-RP accurately channelled 8 CRC patients presenting with anaemia directly to the combined gastroscopy/colonoscopy clinic as TWW while, in reality, they had a tortuous course in secondary care attending multiple clinics before a definitive investigation and diagnosis.

To improve sensitivity, the cancers not assigned by the original e-RP to TWW referral were re-evaluated. A lack of cross-linking of change in bowel habit, rectal bleeding and weight loss was observed. The e-RP was therefore revised and revalidated. This resulted in improvement from 67% to 85% of patients with colorectal cancer being TWW referrals (p=0.002, Chi Square test=9.76, 1 d.f, table 18).

	TWW	*Urgent*	*Routine*	*A&E*	*Internal*	*Other*
Actual	43	22	9	16	9	1
Original e-RP	67	15	7	9	0	2
Revised e-RP	85	1	5	9	0	0

Table 18 Comparison of actual and e-RP (original and revised) for 100 consecutive patients with CRC

4.1.2 Prospective Two-Week-Wait Arm

One hundred consecutive two-week referrals to the colorectal unit were prospectively analysed and processed through the e-RP in the second arm of the study. The definitive outcome for all the referrals was recorded (Table 19). The Lower GI e-Referral protocol only categorised 47% of the referrals as two-week-wait, thus eliminating many benign and normal outcomes from the two-week-wait referral pathway.

Definitive diagnosis	Original e-RP *TWW*	Original e-RP *Urgent*	Original e-RP *Routine*	Original e-RP *A&E*	Revised e-RP *TWW*	Revised e-RP *Urgent*	Revised e-RP *Routine*	Revised e-RP *Referral Advice*
CRC	*8*	*2*	*1*	*0*	*11*	*0*	*0*	*0*
Polyp	*5*	*2*	*2*	*0*	*7*	*0*	*2*	*0*
Benign	*23*	*19*	*7*	*0*	*31*	*11*	*7*	*0*
Normal	*9*	*14*	*5*	*0*	*21*	*3*	*3*	*1*
Other Cancer	*2*	*0*	*1*	*0*	*2*	*0*	*1*	*0*

Table 19 Definitive diagnosis of 100 two-week referrals and e-RP assigned referral grading in them (Pre-revision and Revised). e-RP- "Lower GI e-Referral Protocol"; TWW- Two week wait referrals; A&E- Emergency admissions via Accident and Emergency. Other cancers refer to uterine, ovarian and liver secondaries each.

However, 3 out of 11 CRC patients were downgraded from TWW status to urgent and routine referral with the e-RP. Two patients with rectal cancer had a combination of 'change in bowel habit and weight loss' and 'change in bowel habit and abdominal pain' respectively. One patient with rectal cancer was directed as routine due to anal canal type bleeding and being below 60 years. Subsequent amendments in the e-RP have resulted in upgrading all the colorectal cancers in the second arm of the study as TWW referrals. However, this revision in the protocol has also upgraded 25 benign conditions into the two-week category, but still excludes 28% of benign or normal outcomes from TWW.

4.1.3 Retrospective Routine Colorectal Referral Arm

In the third arm of the study I looked at 100 patients referred routinely to the colorectal unit. These referrals were processed by the e-RP and it successfully upgraded 3 of 4 colorectal cancers, one of them in a large sigmoid polyp (>1cm) to two-week-wait referral status and overall upgraded 21 referrals to the two-week-wait status. One patient aged 40 years with rectal cancer and psychosis had anal canal-type bleeding and the e-RP failed to upgrade this patient to the TWW status. The majority of referrals (69%) were categorised as routine or were categorised for advice from a specialist in secondary care (Table 20).

		Lower GI e-Referral assigned referral urgency of 100 routine referrals						*Total*
		Two-Week Referral	Urgent Referral	Routine Referral	Advice	Improper#	Other Pathway*	
DEFINITIVE DIAGNOSIS	ABSCESS	0	0	1	0	0	0	1
	ANAL POLYP	0	0	1	0	0	0	1
	ANISMUS	0	0	1	0	0	0	1
	CA CAECUM	1	0	0	0	0	0	1
	CA RECTUM	1	0	1	0	0	0	2
	CONSTIPATION	0	0	1	0	0	0	1
	DIVERTICULAR	2	2	3	0	0	1	8
	DNA	0	0	2	0	0	0	2
	FISSURE	1	1	8	0	0	0	10
	FISTULA	0	0	2	0	0	0	2
	IBS	0	1	0	0	0	0	1
	INCOMPLETE	1	0	1	0	0	0	2
	NORMAL	1	4	7	1	1	0	14
	OTHER COLITIS	2	0	0	0	0	0	2
	PILES	6	1	28	0	1	0	36
	POLYPSRECTUM	2	0	1	0	0	0	3
	POLYPSSIGMOID	3	0	1	0	0	0	4
	PROCTITIS	1	0	1	0	0	0	2
	PROLAPSE	0	0	1	0	0	0	1
	SKIN TAG	0	0	4	0	1	0	5
	WART	0	0	1	0	0	0	1
Total		21	9	65	1	3	1	100

Table 20 e-RP assigned outcome of 100 routine referrals.

e-RP could not process faecal soiling as the sole symptom in three patients

* Other Pathway refers to a patient with non-colorectal symptoms

4.1.4 Revision of Clinical Pathways

Initial validation showed deficiencies in the clinical pathways with regard to not only colorectal cancers but also benign low-risk symptoms like anal symptoms, constipation and abdominal pain.

Three out of 11 colorectal cancer patients were downgraded from two-week referral status to urgent and routine referral with the Lower GI e-Referral protocol.

Two patients with rectal cancer among the 100 two-week-wait referrals had a combination of 'change in bowel habit and weight loss' and 'change in bowel habit and abdominal pain' respectively. One patient with rectal cancer was directed via routine due to anal canal type bleeding and being below 60 years.

Necessary refinements were carried out and subsequent revalidation of the same cohort was carried out.

4.1.5 Initial e-Protocol

The initial prototype incorporated the Department of Health high-risk criteria for suspected colorectal cancers. The pathways designed were discriminated mainly by age and family history of colorectal cancer as associated factors. Additional symptoms not in the Department of Health high-risk criteria, like mucous discharge and constipation pathways, were designed in the e-RP to deal with patients presenting with these primary symptoms (table 21).

Table 21 Lower GI Electronic Referral Protocol- Original version (Clustering of primary symptom/sign and associated factors, decide on urgency and referral destination)

Primary Symptom/Sign	Associated Factors	Point of Consultation
Diarrhoea (Age: >60, 40-60, <40)	- Signs of Obstruction - FHx, PHx of CRC	- Emergency Admission - Medical Gastroenterology+- C'Scopy
Abdominal Pain	- Signs of Obstruction - FHx, PHx of CRC	- Emergency Surgical Admission - Medical Gastroenterology
Rectal Bleeding	- CIBH>6weeks - No anal symptoms >60 years - Anal symptoms all ages - FHx of CRC	-Flexible Sigmoidoscopy -Flexible Sigmoidoscopy -Flexible Sigmoidoscopy -Flexible Sigmoidoscopy
Abdominal mass	-Palpable right iliac fossa mass -Possible abdominal mass -FHx of CRC	-Colorectal Surgeons In Clinic -Colorectal Surgeons In Clinic
Rectal mass	-Palpable Rectal Mass -Rectal Examination done -FHx of CRC	-Colorectal Surgeons In Clinic
Constipation	- Signs of Obstruction - Fit for Barium enema (>or 40 years) -FHx of CRC -PHx of CRC -Age below 40	-Emergency Admission -Barium enema in hospital -Medical gastroenterology
Iron Deficiency Anaemia	-Hb<13gm/dl in males -Hb<12gm/dl in females -MCV<76 -Ferritin<15% -Transferrin<15% -Age >80 years, 80 or less -Fitness for C'Scopy	-Colonoscopy &Gastroscopy (fit or below 80 years) -Gastroenterology Outpatient (Unfit, or >80 years)
Mucous Discharge (Large quantities)	-Age>60 -40-60 years -<40 years -FHx Of CRC -PHx Of CRC	-Flexible Sigmoidoscopy

FHx-First degree family history of CRC, age<45 or two first degree relatives with CRC, PHx-Personal history of CRC, C'Scopy-Colonoscopy, CIBH-change in bowel habit to diarrhoea or increase in frequency of stools.

4.1.6 Post Validation Protocol

The initial draft of the protocol incorporated in the "Revive Software" was used to run the validation study using 300 referral episodes. The various outcomes for all the 300 referrals were logged looking at two end points. First we looked at the grading of urgency of referrals by the e-RP and their correlation to definitive diagnosis after investigations. The second end point was to assess the accuracy of referral destination in secondary care by the e-RP. This was compared to preset referral destinations as per local protocols for various lower GI symptoms and signs. The main changes in the protocol subsequent to the initial validation were the following (table 22).

Change in bowel habit and rectal bleed cross-link

The initial validation study revealed a one-sided link of rectal bleed to change in bowel habit (CIBH), but not vice versa on the original e-RP. This was associated with downgrading of less significant pathology like colorectal cancers and inflammatory bowel disease if a change in bowel habit pathway was adopted for symptom analysis. The revised e-RP has these changes incorporated.

Lowering of age of rectal bleeders

The initial e-RP had age >60 years as a criteria for the rectal bleeding pathway and this was in line with the national CRC referral guidelines[243]. However, more than 10 colorectal cancer patients in the validation study were below 60 years. Aiming for a higher sensitivity for CRC to be directed as TWW with the revised e-RP, a lower age group i.e. >50 years was considered acceptable. Four patients (including one rectal cancer) with rectal bleeding were directed as TWW with the revised e-RP from prospective TWW referral arm and 10 patients (including 1 anal polyp, 1 sigmoid and 1 rectal polyp) from the retrospective routine referral group. These extra referrals to be seen on a TWW basis were considered an acceptable trade off to optimize sensitivity of revised e-RP.

Removal of mucous pathway

The mucous pathway was primarily incorporated in the initial design of the e-RP to take account of conditions like villous adenoma of rectum, which can sometimes present with profuse mucous discharge. However, during the initial validation itself, this symptom pathway was never used for any of the 300 referrals, and a decision to remove mucous discharge from the revised e-RP was made.

Addition of anal symptom pathway

While there were no patients with mucous discharge in the validation cohort, there was fair number of patients with anal symptoms of pain, ulcer, suspicious mass etc. To process these patients through the e-RP, I had to design an extra symptom/sign pathway in the revised e-RP.

Lesser role for family history in revised protocol

In line with the current evidence base, a very limited role has been assigned to family history in the revised e-RP, except when it is a first-degree relative aged less than 45 years or two first-degree relatives with CRC[148].

Table 22 Lower GI Electronic Referral Protocol - Revised version (Clustering of primary symptom/sign and associated factors, decide on urgency and referral destination)

Primary Symptom/Sign	Associated Factors	Point of Consultation
Diarrhoea/Frequency	- Signs of Obstruction - Associated Rectal Bleeding - Associated weight loss 3 kg in 3 months - Associated abdominal pain and weight loss	-Emergency Admission -Colonoscopy/Medical Gastroenterology
Abdominal Pain	- Signs of Obstruction - Associated Symptoms CIBH Rectal Bleeding Weight Loss (3 kg/ 3 months) Constipation Anal Symptoms FHx of CRC PHx of CRC	-Emergency Admission -Medical Gastroenterology/C'Scopy
Rectal Bleeding	- Associated Symptom Anal Symptoms (all ages) No anal symptoms (>50 years) CIBH Abdominal pain with Anaemia or weight loss Weight loss 3 kg in 3 months Anaemia (Hb13gm% and Hb12gm%)	- See anal symptom pathway -Flexible Sigmoidoscopy -Flexible Sigmoidoscopy -Flexible Sigmoidoscopy -Flexible Sigmoidoscopy -Flexible Sigmoidoscopy
Abdominal or Rectal Mass	-Abdominal Mass felt -Rectal Mass felt -Possible abdominal or rectal mass Associated.CIBH Associated Weight Loss Associated Rectal Bleeding	-Colorectal Surgeons In Clinic -Colorectal Surgeons In Clinic -Colorectal Surgeons In Clinic
Constipation	- Signs of Obstruction - Fit for Barium enema (>or 40 years) FHx of CRC PHx of CRC - Age below 40	-Emergency Admission -Barium enema in hospital -Medical gastroenterology
Iron Deficiency Anaemia	- Hb<13gm/dl in males - Hb<12gm/dl in females - MCV<76 - Ferritin<15% - Transferrin<15% - Age >80 years, 80 or less - Fitness for C'Scopy	-Colonoscopy & Gastroscopy (fit or below 80 years) -Gastroenterology Outpatient (Unfit, or >80 years)
Anal Symptoms	- Anal Ulcer, Suspicious lesion, Rectal Mass - Weight loss 3kg in 3 months -? Painful fissure - 45 years or over - <45 years	-Colorectal Surgeons In Clinic -Colorectal Surgeons In Clinic -Colorectal Surgeons In Clinic -Flexible Sigmoidoscopy -Rigid Sigmoidoscopy/ Proctoscopy

FHx-First degree family history of CRC, age<45 or two first degree relatives with CRC, PHx-Personal history of CRC, C'Scopy-Colonoscopy, CIBH-change in bowel habit to diarrhoea or increase in frequency of stools.

4.2 Methods - Main Study

The aim was to assess the yield of CRC, whilst filtering less serious pathology such as anal fissure, haemorrhoids, etc, from the TWW and urgent referral system.
To this end, I measured the time periods from referral by GP through first appointment/investigation to definitive diagnosis in groups of patients who were referred using the e-referral protocol (e-RP) or through traditional referral methods.

The Process And Evolution Of This Study's Design

The study's design was principally collaboration between the Department of Colorectal Surgery, Royal Bournemouth Hospital, the University Department of surgery, Southampton General Hospital, the Southampton Public Health Sciences and Medical Statistics Department and Poole Research and Development Support Unit (RDSU). Time was taken to visit a NHS trust in Crewe, where significant work on colorectal referral pathways had already been done, in order to understand the set up, data collection, coordination of outpatient and endoscopy departments and associated resource implications.

Prospective

In order to accurately compare the strategies of GPs referring directly to colorectal and gastroenterology services in this single secondary care centre and those using the e-RP, a prospectively designed parallel pragmatic trial was designed. The use of historical controls or changing management strategies in the hospital can expose all data to distortion and inaccuracies, hence a parallel design was chosen. Prospective study design ensured minimal recall bias and selection bias, as would be expected of a case control study.

Consideration for Randomisation

Though randomisation, either at patient, General Practitioner or general practice level, would have helped to minimise bias, the difficulties encountered in trying to implement such a design were huge.

1. Individual patient randomisation would have been the best design to minimise bias and was considered, but quickly dismissed, as it was felt to be impossible to have two systems (e-RP and non e-RP) running under the care of the same doctor.
2. We encountered difficulties in terms of the willingness and consent of General Practitioners to be randomised, and it was clear that these were influenced by several factors including the age of the doctor, IT skills, desire to take part in the trial and overall fear of litigation and/or indemnity cover if patients are

disadvantaged through either route.

3. The option to randomise general practices individually or as a cluster was considered. However, statistical advice was received that a minimum of 20 practices in each arm of the study would be required for cluster randomisation, and the feasibility of getting this number was questionable. With the number of practices likely to take part, intra-general practice variability in the use of referral guidelines would certainly confound the results in spite of cluster randomisation[192].
4. The national Choose and Book programme, where the e-RP has been created and installed, has been introduced in a sequential manner in general practices, due to logistics and training issues. This would have made a randomised trial with a fixed start date difficult due to sudden changes in the GPs' referral practices, the slow learning curve, and variability between GPs.

Because of these difficulties, and after much consideration, it was decided to run the study as a natural experiment, and to allocate participating practices to the intervention on a "first come, first served "basis.

The e-RP was incorporated as a local bolt on to the national Choose and Book Programme, active from desktops online while General Practitioners were using the Choose and Book referral system. The overall study period was originally scheduled to run from mid-February 2006 to November 2006, if a sufficient amount of significant pathology was received through the e-RP to arrive at statistical conclusions. General practices in Bournemouth PCT and South and East Dorset PCT were invited to participate in the trial. Twenty general practices spread over two Primary Care Trusts accepted the invitation for the trial in the use of the e-RP. The patients referred from the other 27 practices in the Bournemouth Teaching PCT and South & East Dorset PCT were also logged in the database.

4.2.1 Questions Posed By This Study And Hypothesis

Can a validated e-RP influence the yield of CRC coming through the TWW system? Can e-RP deal with the appropriate referral destination in secondary care?

Null Hypothesis

The Lower GI e-Referral Protocol in primary care will not influence the referral process to secondary care in patients with colorectal symptoms and suspected anaemia; in particular, time periods from referral to diagnosis and appropriateness of the specialist team seen in secondary care.

Specific Questions

1a. Can a valid Lower GI e-Referral Protocol in the primary care setting improve the yield of CRC from the two-week-wait referral system?

1b.Will the Lower GI e-Referral Protocol direct patients with lower GI symptoms into appropriate patient pathways e.g. gastroenterology clinics, colorectal surgical clinics, endoscopy, direct access barium enemas, and colonoscopy?

1c. Will the use of the Lower GI e-Referral Protocol support GPs in referring less serious pathologies along less urgent routes?

1d. Will the above measures improve outcomes in terms of time periods, appropriate patient pathways, disease stage and GP satisfaction?

Primary Outcome Measures

Outcomes of validated electronic lower gastrointestinal protocols for referral and decision support in primary care were compared with respect to:

1. Yield of significant pathology (CRC) from the Lower GI e-Referral Protocol (e-RP) referral group compared with conventional referral in secondary care.
2. Accuracy of destination of referral pathway in the e-RP group and conventional referral group for CRC was compared.

Secondary Outcome Measures

1. Time periods from referral, through diagnosis and treatment, were compared in both groups in relation to significant pathology (CRC).
2. Referral urgency and route of benign colorectal diseases, excluding cancer were compared in the two arms of the study.
3. Logistics, sensitivity and specificity of the Lower GI e-Referral Protocol were assessed.

4.2.2 Setting For The Study

This prospective, parallel, non-randomised trial looking at the benefits of a dedicated Lower Gastrointestinal e-Referral Protocol was carried out primarily involving one secondary care hospital (The Royal Bournemouth Hospital), and general practices in the Bournemouth and South & East Dorset Primary Care Trusts.

General Practices

There are **24 general practices in Bournemouth PCT** with an overall population of 172,964 (2005-2006, Quarter 2). These practices all refer to the Royal Bournemouth Hospital.

There are **23 general practices in South & East Dorset PCT** sub-divided into 3 regions and straddling Bournemouth and Poole PCTs from east to west. Because of this straddling it is often called the "banana republic".

The three regions are,
Christchurch region – 7 general practices and a population of 52,735
Purbeck region – 6 general practices and a population of 33,512
East Dorset region – 10 general practices and a population of 69,001
(2005-2006, quarter-2).
The Purbeck region lies to the west of Poole and conventionally refers patients elsewhere. The practices in the Christchurch area refer to Royal Bournemouth Hospital. Most of the East Dorset practices refer to Royal Bournemouth Hospital.

Hospital

The Royal Bournemouth Hospital is a secondary care hospital with Foundation status forming the NHS trust along with Christchurch Hospital. The 800-bed RBH caters to most disciplines of medicine and has a fully-fledged lower gastrointestinal surgical unit comprising three consultant surgeons and junior medical staff, in addition to two colorectal nurse specialists and two stoma sisters. This unit is well supported by an endoscopy department and gastroenterology unit, and the services offered include, diagnostics and treatment of lower GI pathology, as well as radiology and oncology services.
All CRC go through the Cancer MDT before treatment is instigated in elective patients.

4.2.3 Inclusion & Exclusion Criteria

The inclusion criteria were defined separately for GPs and for patients at the trial design stage.

GP and general practice criteria and allocation to study groups

General Practitioners who gave informed written consent to participate in the trial were included. They were allocated into groups according to their response to our invitation to take part. Eleven general practices in their initial meeting with us agreed to take part in the trial and the GPs signed the consent form.

These practices used the e-RP for the period of the trial. Nine general practices required further visits before consent was forthcoming. These practices did not use e-RP until after the trial period was over. All 20 General Practices had equal educational input regarding the e-RP and were in the same demographic areas within Bournemouth and South East Dorset PCT. We also collected data on those practices, which had not agreed to meet with us, giving us three groups for analysis at the end of the study period.

1. General practices with training and access to e-RP in the Bournemouth PCT and South & East Dorset PCT and using e-RP ***(Pilot Sites using e-RP)***.

2. General practices with training and access to e-RP in the Bournemouth PCT and South & East Dorset PCT and not using e-RP ***(Pilot Sites not using e-RP).***

3. General practices without training or access to e-RP in the Bournemouth PCT and South & East Dorset PCT ***(Non-Pilot Sites).***

Patient criteria

- Adults (>18 years) referred with colorectal symptoms/signs to secondary care, who consented to participate in the trial.

- Adults (>18 years) with possible iron deficiency anaemia for evaluation (Haemoglobin <13 gm% in males and Hb<12 gm% in female patients) who consented to participate in the trial.

Exclusion criteria

Patients with an established diagnosis of colorectal cancer under investigation, treatment or follow up were excluded.

4.2.4. Referral From Primary care

Referrals made by GPs

All referrals from General Practitioners to the six consultants (three Colorectal and three Gastroenterology) in Royal Bournemouth Hospital were logged after filtering out non-colorectal patients.

Suspected iron deficiency anaemia patients were also logged in for this study in addition to colorectal referrals. This was possible by designing seven colorectal/IDA self-inking stamps for the six consultants and the research fellow (fig 10). The purpose was to sort the referrals appropriately.

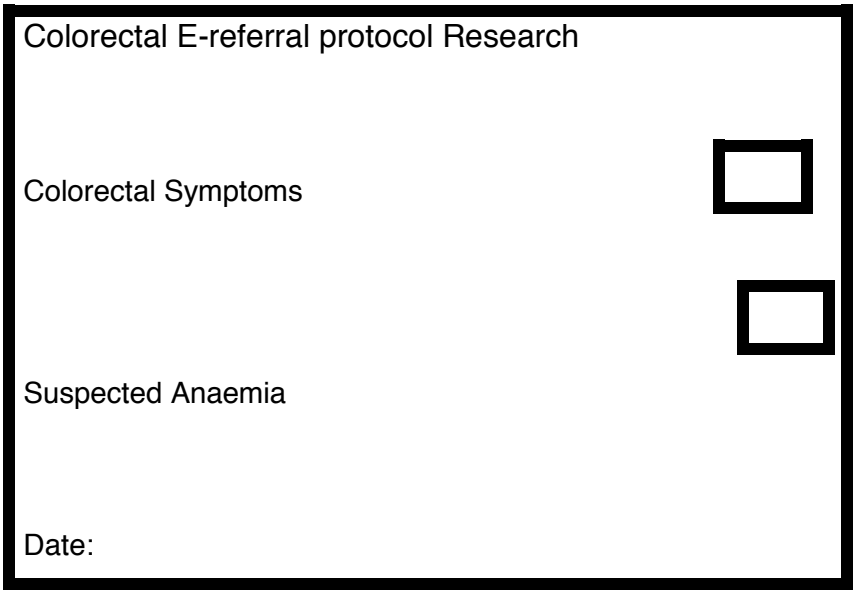


Figure 10 Prototype design of the large rubber stamp

The referrals from each general practice were included in the trial after the practice meetings when consent became available from the General Practitioners in the Pilot arm of the trial.

Referrals made to Consultants

The consultants had the inclusion criteria as a wall poster over their desks, and the rubber stamp was made available with the pile of new referrals to ensure its regular use. The secretaries and research fellow reminded the consultants of the procedure in the initial phase of the trial. All GP referrals to the consultants except the TWW referrals and the e-

RP referrals were sorted out. Consultants did not grade the referrals through the e-RP, so the e-RP-assigned urgency of referral and the referral destination remained sacrosanct.

Logging of referrals (Non-TWW)

The consultant-stamped GP referral letters were photocopied and filed by the research fellow. The original stamped letter was sent to clerical staff at outpatients and endoscopy where, under the close supervision of the outpatients booking manager and endoscopy appointments manager, the invitation to participate in the trial, the patient information sheet and the consent form were sent with a prepaid (second class stamped) return envelope.

This strict protocol was ensured after thorough education of the staff in both these departments. The research fellow ensured, initially on a weekly basis and then once every two weeks, that the process was up to speed and any glitches were being addressed appropriately and promptly. All the paperwork mentioned was sent, along with the patient's appointment letter for outpatients, or Straight to Test as per the consultant's redirection of the GP's referral destination (except for TWW and e-RP referrals).

Logging of TWW referrals

All TWW colorectal and suspected IDA referrals from the Bournemouth and South East Dorset PCT were initially logged by the fast-track (TWW) coordinator and copied to the research fellow.

Grading of Referrals

The consultants had the option to grade the urgency of all referrals except the TWW and e-RP referrals. They could assign urgent or routine status to a non TWW referral and indicate whether the consultant wanted to see the patient in e.g. the Rectal Bleeding Clinic, Outpatients Department, Barium Enema or Colonoscopy etc.

Excluded from Analysis

In this trial, as we were comparing referral pathways from primary care, all internal referrals from other departments had to be logged but excluded in the analysis. Similarly, referral letters with incomplete information, referrals without returned consent forms, those where the identity or the source of referral were unclear and those where the referrals were not from the two PCTs in the trial, were excluded in the analysis.

Roles of Other Staff

The nature and design of the trial post-LREC modification did create significant logistical difficulties in organisation, including poor anticipation of the amount of clerical and

secretarial help that would be required at the start of the study. However, necessary measures were in place to account for the extra workload imposed on the fast-track co-ordinator, secretarial staff and the Outpatient electronic Booking manager. There were printed posters exhibited in the outpatient's consultation rooms and endoscopy department during the period of the trial. The nursing staff involved with these patients were fully informed of the trial. It was only occasionally that staff needing further information to explain the study to patients contacted me.

Data Collection

The data collection was started in February 2006 and continued until January 2007. This was the actual trial period when all referrals meeting the criteria mentioned earlier were collected.

Filing of Referrals

The referrals were entered into a database linked to the Patient Management System (PMS) of the hospital. All the referrals were then filed, based on whether they came from Pilot sites with or without e-RP or Non-Pilot Sites. The referrals made through the e-RP were separately filed.

Entry into the database

The creation of drop-down menus in most fields of the database helped to speed up data entry, along with links to the ACPGBI colorectal cancer database. Two junior doctors assisted with this in the earlier phase of the trial; in the latter part the colorectal MDT coordinator helped with data entry.

Coding of data

All variables in the Windows Access database were numerically coded with drop-down options on a single click, to fill the database easily and quickly.

Definitive diagnosis codes

Those with normal colonic evaluation were coded as **'Normal study'**. All other codes were synonymous with the diagnosis mentioned in table 23.

'Incomplete' - This code was used for mostly frail, elderly patients unfit for tests. Few patients awaiting tests had to be coded as incomplete, in spite of over 5 months waiting for outcomes in these patients (February 15th 2007 to July 25th 2007).

'DNA' - (did not attend). These were patients who had failed to attend the first appointment or further appointments for tests and had not contacted the secondary care hospital.

'Cancelled'- Most of these patients had either moved to another place or provider, or called in and cancelled appointments.

'Other Lower GI'- This group comprised patients with variety of less-common lower gastrointestinal pathology including, faecal incontinence, irritable bowel syndrome, rectal prolapse, warts, fistulae, coeliac disease, pilonidal/perianal sinus, perianal skin tags, volvulus, parastomal hernias, pruritus ani etc.

1	Normal Study
2	Incomplete
3	DNA-Did Not Attend
4	Cancelled
5	Ca Anal canal
6	Ca Rectum
7	Ca Sigmoid
8	Ca L colon
9	Ca T Colon
10	Ca H Flexure
11	Ca S Flexure
12	Ca R Colon
13	Ca Caecum
14	Diverticular Disease
15	Polyps >1cm
16	Polyps<1cm
17	IBD
18	Other Colitis
19	Other Lower GI
20	Upper GI
21	Non GI Pelvic
22	Non GI RetroPeritoneal
23	Piles
24	Fissure
25	Ca Appendix
26	Ca Lung

Table 23 Coding of definitive diagnosis

Coding of Time Periods Utilised

Delays were calculated based on two time periods i.e. 'referral to first appointment' (a better reflection of GP practice) and also 'referral to definitive diagnosis' the best indicator of delay if a patient with significant pathology like CRC is placed in appropriate clinical/investigation pathways.

The time periods recorded for 'significant pathology'

1. Date of referral: Available on the Choose and Book website for all Choose and Book referrals. For referrals through the e-RP, the date of the secure e-mail generated was taken as the referral date. Paper referrals had referral dates available.
2. The date of the first appointment in secondary care (Outpatients or Straight to Test) was recorded, based on the clinic letter or Straight-to-Test result generated and available from the secure hospital intranet (E-Camis).
3. Date of definitive investigation: either colonoscopy or barium enema dates or, where deemed adequate by a consultant surgeon or consultant gastroenterologist, flexible sigmoidoscopy dates.

The time periods calculated were

Referral to appointment

Referral to definitive diagnosis

Though similar analysis was attempted of the non-significant pathologies in both arms of the study, due to the higher proportion of missing values [DNA, incomplete episodes, cancelled appointments etc], the relevance of the analysis was dubious.

Completeness of Data Collection

Data entry was ongoing from the start of the trial. Its completeness was ensured by repeated cross checking with paper forms filed and entries in E-Camis, and the dataset was finally updated in the 3rd week of July 2007, prior to the research post finishing.
All patients with 'significant pathology' i.e. colorectal cancers were doubly crosschecked with the ACPGBI dataset maintained by the Cancer MDT office.

4.2.5 Statistical Analysis

All statistical analysis was carried out on SPSS v.14. The various parametric and non-parametric tests applied depended on the variable analysed and the distribution of data. Statistical input from University of Southampton and from the Research Development Support Unit (RDSU) at Poole also helped in data analysis. P values of 0.05 or less were considered significant.

For the statistical analysis of the "delays", the data for "referral to appointment" and "referral to definitive diagnosis" was initially plotted as a histogram. Significant right skewing was noted in all the datasets for "delays".
Log 10 transformation of these data was carried out prior to comparing means using independent samples t tests.

4.2.6 Secondary Care Organisation

Any service delivery issue studied as part of a trial requires considerable time and effort, the introduction of new resources and the reconfiguration of existing services. The concept of using e-RP for referral of patients and analysing the outcomes involved addressing such factors in both primary care and secondary care. In primary care, both GPs and clerical staff required training and education. In the hospital, various departments including Information Technology (IT), Endoscopy and Outpatients required training input for clerical and nursing staff. Active involvement and awareness among medical staff in colorectal surgery and gastroenterology was necessary for the trial and I coordinated all these various activities.

The trial was initially planned to start in August 2005, when local GP surgeries did not yet have Choose and Book facilities. The initial e-RP was therefore designed in the Revive software used for decision support.

The initial submission to the Local Research Ethics committee resulted in rejection of the research protocol. The need to revise the research protocol and design of the trial delayed the project for over four months before LREC; primary care and secondary care R&D approvals came through in December 2005. The major changes required were to do with consenting of patients in primary care by GPs. This was not considered a feasible option and the decision was made to recruit general practices and consent patients once they had been referred to secondary care by the research team. This was fortuitous, as significant changes occurred in this time period, such as the Government's decision to introduce Choose and Book nationally and to fix incentive-based targets for its use by PCTs and General Practitioners.

This led to a decision to incorporate the e-RP as a local bolt-on to the national Choose & Book programme, so the time spent waiting for primary care R&D approval from two PCTs was used to overcome a limited knowledge of Choose & Book and the lack of clear advice on using it to design an e-RP.

Service Development Team Input

Continued dialogue with national coordinators by the hospital service development team, finally led to an option to design and use e-RP in the Service Selection & Booking Guidance facility of Choose & Book. As this was the first instance of using e-RP on Choose & Book nationally, and no similar protocols had been designed previously, it was a continuous challenge with the limited software flexibility offered by Choose & Book.

Design of e-RP on Choose and Book

As a first step, a template of e-RP was designed in the colorectal speciality site of Bournemouth PCT. The obvious problem was how to capture the information as to whether the General Practitioner would use e-RP or not, as Choose and Book didn't have an automatic facility to record the use of e-RP by the GP prior to the referral of a patient from primary care. We had further discussions with national coordinators and local primary care cancer leads, and finally decided to use a secure e-mail option as hypertext inserted in the outcome page of e-RP on Choose and Book (see appendix for e-RP outcome page). The GP had the option to go with e-RP decision support or override it; in either case a specific very secure email would have to be sent by the GP to the primary researcher (myself). This would contain essential patient details, the referral destination and the level of urgency of referral designated by e-RP.

IT Input

Any project of this nature, involving links between primary care and secondary care, requires very good IT backup and infrastructure. The constant involvement of the hospital IT department in the initial stage of the study hastened the development of e-RP, setting up a parallel database similar to the Association of Coloproctology's database, with links to the hospital's Patient Management System, automatically downloading patient demographics.

The primary researcher was given access to a secure drive on the Cancer Database in the hospital intranet, which is automatically backed up every day. I was also provided with a laptop funded by the Surgical Directorate to carry out all my writing and data-entry activities. The help of the IT technicians was sought in creating queries to interrogate the database in the data analysis stage of the main study.

Restructuring of Services

Grading of Referrals to Gastroenterology and Colorectal Surgery

All patient referral letters except for the TWW referrals (colorectal, gastroenterology and iron deficiency anaemia) are graded by consultants as 'Routine', 'Urgent' or 'Soon' and 'TWW' in this secondary care centre. As part of the trial, the referrals made by GPs through e-RP were exempted from the grading process. This ensured that the ability of e-RP to self-grade referrals could be assessed independently.

Contingency plan in Endoscopic Services for the trial

Endoscopy services were aware of the implications of the trial and were ready to open extra lists for flexible sigmoidoscopy and for colonoscopy if need be. The colonoscopy list was independent of the IDA (iron deficiency anaemia) combined gastroscopy and

colonscopy list that already existed. The primary researcher independently carried out flexible sigmoidoscopy on a weekly basis and extra lists as required to help with the potential extra workload anticipated with this trial.

Accommodation of possible extra GP-booked barium enemas

The radiology department was similarly aware of the implications of the trial, especially the facility to book barium enemas directly, either as TWW, as urgent or as routine by GPs when using the e-RP. The radiology directorate agreed to this in the initial design phase of the e-RP itself. Barium enema due to its lower sensitivity and specificity for colorectal cancer diagnosis was mainly linked to low risk symptom complexes for CRC in the e-RP.

4.2.7 Primary Care Organisation

First Invitation to take part in the Study

General practices in Bournemouth Primary Care Trust were sent letters from the Colorectal Cancer Lead of Royal Bournemouth Hospital inviting them to take part in the trial from July 2005 onwards. The decision to send invitations to practices in this PCT was guided by the previous use of electronic referral by GPs in these practices. Eleven of the general practices agreed to take part, and a date and time for the introductory meeting was fixed with practice managers.

Looking at the general practices that responded positively to the invitation revealed little or no association to the previously better-performing general practices referred to in Chapter 2 and Fig 7(Scatter plot).

Second Invitation to take part in the Study

Primary care R&D approval from both Bournemouth and South East Dorset PCT prompted us to invite more general practices into the trial. Nine general practices were recruited in this round (Table 24), seven from East Dorset and a further two from Bournemouth, after open invitations for the study were sent to all general practices.

GP Practice	PCT	Consent Meeting	Number of GPs Consented
Leybourne	BPCT	16/01/2006	2
Southbourne	BPCT	08/02/2006	5
Mooredown	BPCT	16/01/2006	4
Denmark	BPCT	09/01/2006	4
Stour	SED PCT	23/06/2006	5
Orchard	SED PCT	22/06/2006	6
James Fisher	BPCT	30/01/2006	9
The Village	BPCT	12/12/2005	4
Holdenhurst	BPCT	13/04/2006	3
Littledown	BPCT	16/03/2006	3
St. Albans	BPCT	16/12/2005	5
Gervis Road	BPCT	19/05/2006	6
Alma Road	BPCT	04/04/2006	5
Banks Surgery	BPCT	18/04/2006	4
Northbourne	BPCT	07/04/2006	4
Orchid House	SED PCT	28/06/2006	6
Penny's Hill	SED PCT	22/05/2006	5
HighCliffe	SED PCT	01/08/2006	6
Corbin Avenue	SED PCT	22/07/2006	2
Burton	SED PCT	09/06/2006	6

Table 24 List of General Practices, start date (consent date) & GPs Consenting

General Practice Meetings

An initial meeting was set up in each general practice that had expressed an interest in the study. The primary researcher, accompanied by one of the two colorectal surgical consultants subject to their daily schedule, carried out the initial visit.

Colorectal symptoms, signs and the current low yield from the TWW system were discussed in length and PowerPoint presentations given. The performance of individual Pilot Sites in previous years (Chapter 2) was shown anonymised, and the interpractice/intrapractice variability in colorectal referrals was highlighted along with the survey results (Chapter 2).

The current literature on these topics was discussed, and written handouts of the trial, the patient information sheet, with both patient and GP consent forms, were provided in individually named folders for each GP (See Appendix B for tutorial notes on the trial, PIS, Patient and GP Consent Form). The validation study (section 4.1) was presented to the GPs and their questions answered. Finally, a demonstration of e-RP on Choose & Book was carried out. Any queries on e-RP or on colorectal referral pathways were addressed

in each meeting.

General practitioners from the pilot sites were equally trained in use of e-RP, whether they formed part of the group allocated to using it over the trial period or not, and had the same educational input.

Further General Practice Visits

Further visits by the primary researcher were carried out in the second month and then in the sixth month. These meetings were pre-arranged with the practice managers, either during weekday lunchtimes or on an evening in some general practices, and usually involved further discussions and updating on the trial. Major issues pertaining to e-RP were addressed or logged for further attention. In the interim period most communications were via e-mail to the primary researcher. The consultant colorectal surgeons took part in a few of the latter practice visits as well.

Reminders to GPs

Individual reminder letters were sent to each General Practitioner consenting to the trial during months 4 and 8 of the study. The intention was to keep interest in the trial going, and corresponded to the period when practice visits were not being done (2^{nd} & 6^{th} months).

Communication to all GPs in two PCTs

LREC stipulations required all GPs in the Bournemouth Teaching PCT and South & East Dorset PCT to be aware of this trial and to have received a copy of the patient information sheet and patient consent form irrespective of being in the active e-RP arm of study or not. This was because all patients referred to secondary care who met the inclusion criteria would be sent a patient information sheet and consent form and it was important that their GPs were aware of their patient being involved in a study.

4.2.8 Setting The Endpoint For The Study

All studies need an endpoint, a specific event against which measurements can be made. Many medical trials assessing the effects of treatment employ patient death as a valid and easily defined endpoint. However, in this trial, which is not concerned with survival, an acceptable alternative needed to be found, and this was mainly guided by the aims mentioned in section 4.2.1. An endpoint should be clearly and simply defined, should be relevant to the intervention being measured, and should be identifiable for all patients. Endpoints were defined as:

1. Receipt of a **'definitive diagnosis'** if no treatment is required (As mentioned in the clinical records after the referral episode to the secondary care either post-

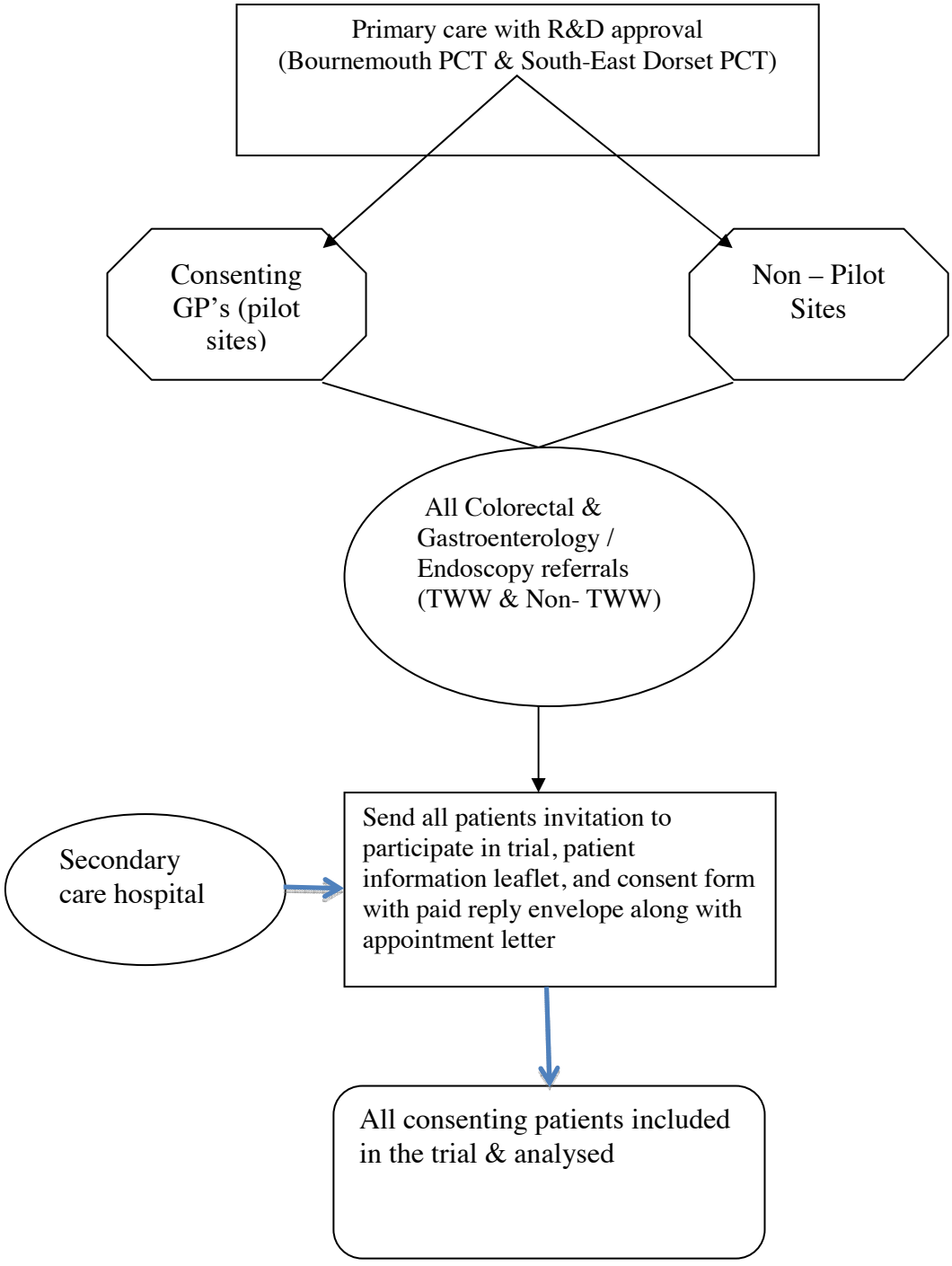
investigations, or documented clinical diagnosis if no investigations are planned).

Or

2. Definitive treatment received

4.2.9 Logistical Issues

The design, and later modification as per LREC stipulation, imposed few logistical difficulties in getting the trial running. The LREC direction that *"all patients referred to colorectal and gastroenterology services had to be sent a patient information sheet and a consent form along with their appointment letter"* created a some workload for the clerical side of the endoscopy and outpatient booking departments. Two dedicated staff ensured that this was done.



4.2.10 Sample Size

No previous similar work has been published that might have assisted us in arriving at any predetermined power/sample size.

From data relating to 2003-2004, we knew that there would be approximately 26 cases of cancer from 7 practices using the protocol, and 66 cases from the 17 control practices in the Bournemouth PCT. Previous data has shown that the sensitivity of GPs correctly fast-tracking patients was 24%. With this sample size the study would have 11% power to detect a 10% improvement, 37% power to detect 20% improvement, 70% power to detect a 30 % improvement and 92% power to detect a 40% improvement. Initial estimates suggested that an improvement of over 40% might be realistic, based on the 85% sensitivity seen in the validation study. A 5%, 2-sided significance level was used for the calculation.

We later estimated that the main study, with 20 general practices in the e-RP arm, would yield approximately 72 CRC in a year through the TWW route. Assuming equal numbers of cases in each group this gave us 90% power to find the 40% difference specified above.

4.2.11 Study Site Approvals

Ethical approval for the study

Full ethical approval for the study was obtained from the Dorset LREC in November 2005. This was after amendments to the trial design. The initial design of the study involved consenting General Practitioners in both arms of the study. Since patient data was only to be looked into for analysis and no direct patient intervention planned, this was considered an acceptable trial design, but the issue of consenting patients, either in primary care or in secondary care, lacked clarity and the LREC rejected the initial protocol. This design was considered unacceptable and consent was required from individual patients in addition to the General Practitioners. Lack of GPs consenting patients would leave us with low power to the study. This required modification to the trial design (see flow chart in Logistics section). Minor changes in the wording of the patient information leaflet were carried out as well.

R&D Approval from Primary Care and Secondary care

Indemnity was a pressing issue with GPs, responsible for over two months delay to the start of the trial. The Bournemouth PCT and South & East Dorset PCT finally approved the study in addition to Royal Bournemouth Hospital & Christchurch NHS Trust indemnity cover (trust peer review: MWP/065/05).

Data Protection Act

As part of the LREC's requirement, the Royal Bournemouth & Christchurch NHS Trust's Data Protection Officer and Caldicote Guardian were informed of the study's aim, purpose and design (DATA PROTECTION ACT No: 156). The Data Protection Officer is charged with ensuring ongoing research meets with the Trust's responsibility to conform to the Data Protection Act.

Audit And Clinical Effectiveness No: 083/05

Approval from the Royal Bournemouth & Christchurch NHS Trust's Clinical Effectiveness and Audit Departments was also required to run the trial. The Audit Department played an important role in getting the two GP surveys done under my supervision.

5 Results From The Main Study

One of the main determinants for an increase in colorectal cancer yield is the age of patients being referred. The first analysis of the raw data was to look for any major differences in the mean age in the various groups.

Group 1: Non-Pilot Sites (general practices with no access to e-RP and no direct educational input). This group is not part of the main comparison but serves as a comparator for the educational input received by both pilot groups

Group 2: Pilot Sites not using the e-RP (general practices not using e-RP, but receiving the direct educational input).

Group 3: Pilot Sites using e-RP (general practices using the e-RP and receiving direct educational input).

Groups 2 and 3 form the main comparator groups for the main study.

The histograms (fig 11) with normal curves superimposed show that all groups had a similar near-normal age distribution, with some preponderance of older age bands across all three groups.

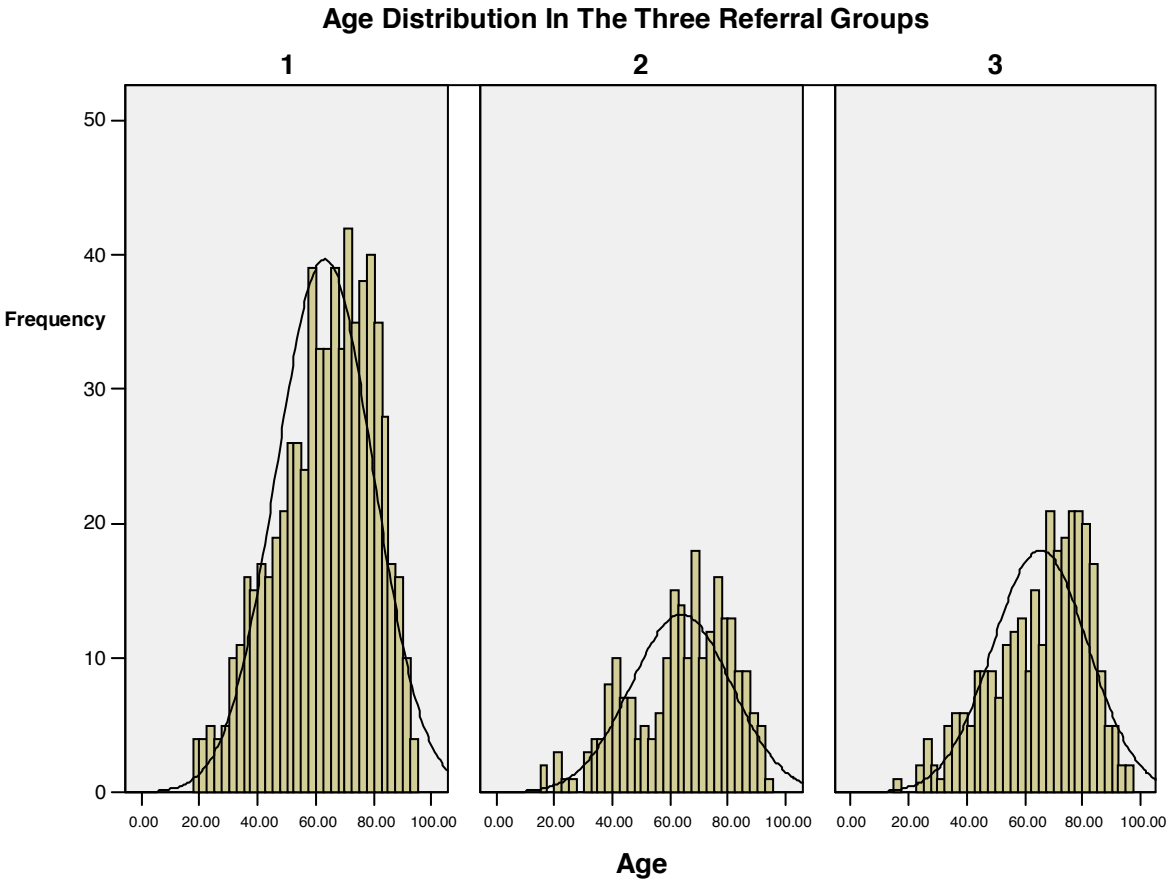


Figure 11Histogram of age (in years) in three groups

Group 1 Non-Pilot Sites

Group 2 Pilot Sites (not using e-RP)

Group 3 Pilot Sites (using e-RP)

Comparing mean ages with Independent Sample t-test between each two groups revealed a few interesting observations.

Group 1 & Group 3: There was slight difference in the mean ages in these two groups. Group 1 (Non-Pilot) 63.2 years, and group 3 (Pilot Sites using e-RP) 65.5 years (t-test -2.015, p=0.044; CI of difference of mean -4.61 to -0.061).

However, comparison between other groups was statistically insignificant.

Group 2 & Group 3: These two groups comprise the two main groups for further analysis in this thesis Mean ages 63.9 and 65.5 years,(t-test -1.101, p=0.271; CI of difference of mean -4.52 to 1.27)

Group 1 & Group 2: Mean ages 63.2 and 63.9 years

(t-test -0.552, p=0.581; CI of difference of mean -3.42 to 1.82)

Gender distribution in the three groups

Overall no significant differences were noted for male/female distribution in Group 1 (Non-Pilot Sites) and Group 3 (Pilot Sites using e-RP).

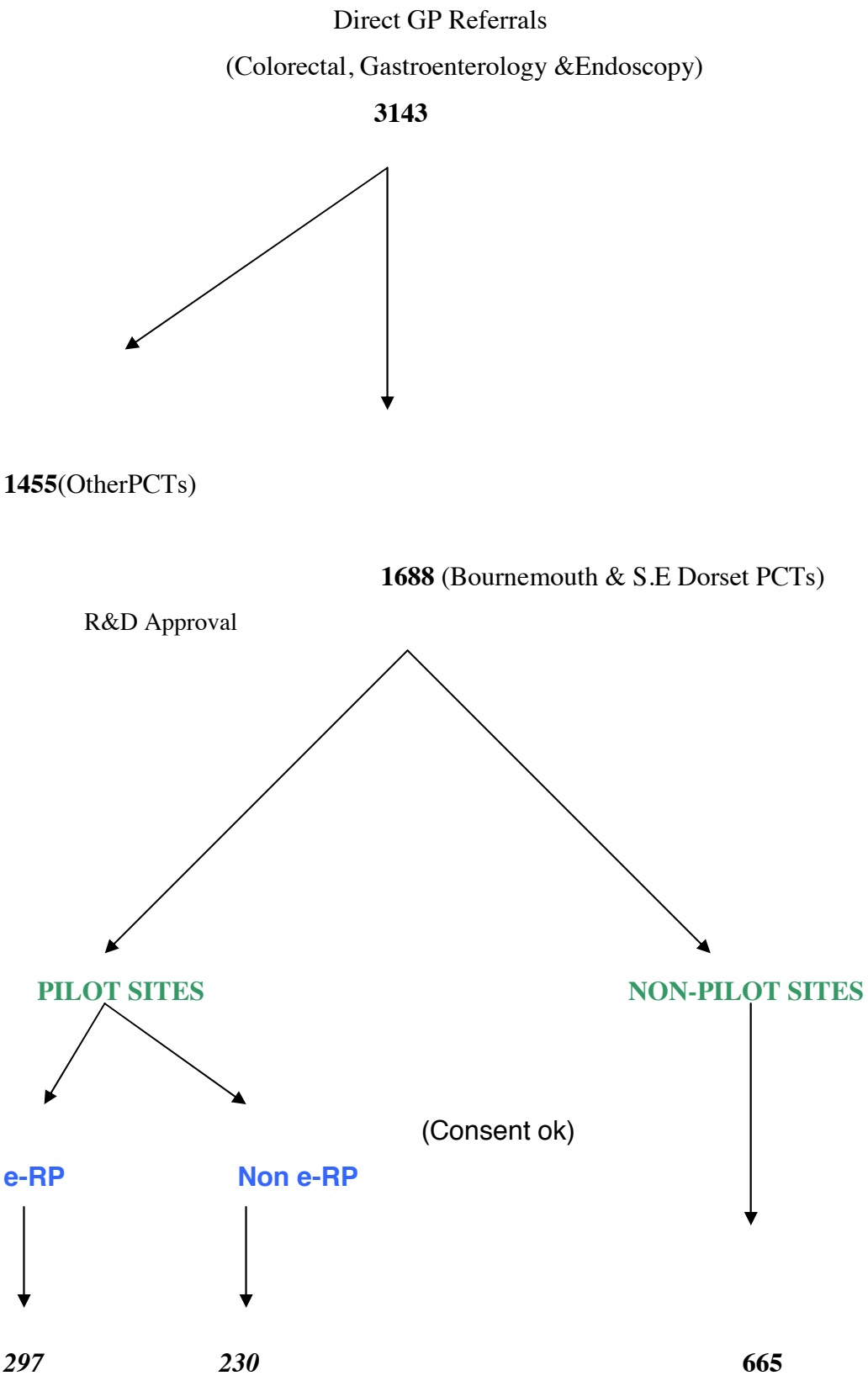
However, Group 2 (Pilot Sites not using e-RP) had more than twice as many female patients as male patients. This resulted in a significant difference on Chi square test. (See table 25).

		Three Groups			*Total*
		Non-Pilot Sites	Pilot Sites (Non e-RP)	Pilot Sites (e-RP)	
Sex	Male	310	68	144	522
	Female	355	162	153	670
Total		665	230	297	1192

Table 25 Sex distribution in the three groups (Chi square 23.725, p=0.000, df-2)

Flow Chart of Recruitment for the Main Study

(Data Collection Feb 15th 2006 to Jan15th 2007)



Exclusions:

A) No Consent:

26 e-RP Referrals

421 Other Referrals

B) No Patient Details in e-RP arm: 20 referrals

C) Source of Referral Unclear: 29

The main study compares the **297 patients** referred from primary care through e-RP and the **230 patients** referred from pilot sites not using e-RP.

Definitive diagnosis

Number and percentages of definitive diagnosis for patients referred through all routes (e-RP, Non-Pilot Sites and Pilot Sites not using e-RP) are given below in table 26.

Final Diagnosis	*Routes of Referral*			*Total*
	Non-Pilot referrals	Pilot Sites not using e-RP	e-RP referrals	
Ca Appendix	0(0)	0(0)	2(0.7)	2(0.2)
Ca Caecum	3(0.5)	1(0.4)	4(1.3)	8(0.7)
Ca Right Colon	3(0.5)	2(0.9)	1(0.3)	6(0.5)
Ca Hepatic Flexure	0(0)	0(0)	1(0.3)	1(0.1)
Ca Transverse Colon	3(0.5)	0(0)	2(0.7)	5(0.4)
Ca Descending Colon	2(0.3)	0(0)	0(0)	2(0.2)
Ca Sigmoid Colon	9(1.4)	3(1.3)	4(1.3)	16(1.3)
Ca Rectum	11(1.7)	3(1.3)	11(3.7)	25(2.1)
Polyps >1cm	20(3)	6(2.6)	9(3)	35(2.9)
Polyps < 1cm	34(5.1)	10(4.3)	20(6.7)	64(5.4)
IBD	20(3)	6(2.6)	8(2.7)	34(2.9)
Other Colitis	10(1.5)	10(4.3)	13(4.4)	33(2.8)
Diverticular Disease	37(5.6)	12(5.2)	36(12.1)	85(7.1)
Piles	91(13.7)	25(10.9)	48(16.2)	164(13.8)
Fissure	19(2.9)	5(2.2)	4(1.3)	28(2.3)
Other Lower GI	40(6)	10(4.3)	11(3.7)	61(5.1)
Upper GI	22(3.3)	5(2.2)	11(3.7)	38(3.2)
Non GI Pelvic	6(0.9)	1(0.4)	2(0.7)	9(0.8)
Non GI Retro peritoneal	2(0.3)	0(0)	3(1)	5(0.4)
Ca Lung	0(0)	1(0.4)	1(0.3)	2(0.2)
Normal Study	260(39.1)	102(44.3)	80(26.9)	442(37.1)
Incomplete	13(2)	8(3.5)	15(5.1)	36(3)
DNA	14(2.1)	7(3)	7(2.4)	28(2.3)
Cancelled	46(6.9)	13(5.7)	4(1.3)	63(5.3)
Total	**665(100)**	**230(100)**	**297(100)**	**1192(100)**

Table 26 Number and percentage of definitive diagnosis (% of column) for all referrals

Distribution of definitive diagnosis

All the groups had a grossly similar distribution of definitive diagnosis (table 27) and there was no statistically significant difference (Chi-square 8.178, p0.085, df 4).

		Distribution of Definitive Diagnosis			
		CRC	Benign & Normal study	Incomplete, DNA, Cancelled etc	Total
Three Groups	Non-pilot referrals	31	561	73	665
	Pilot sites not using e-RP	9	192	29	229
	e-RP referrals	25	246	26	297
	Total	**65**	**999**	**128**	**1192**

Table 27 Distribution of definitive diagnosis in three groups

5.1 Yield of e-RP For Significant Pathology

The yield of colorectal cancers in the secondary care hospital were taken as outcome measures to calculate yield of the e-RP referral pathway against the pilot sites not using e-RP. The patients in the incomplete, DNA, cancelled group (see table 28) were excluded from the analysis.

The yield of e-RP was 9.2% (25/271) for CRC compared to a yield of 4.4% (9/201) in the pilot sites not using e-RP. This was found to be significant statistically (Fisher's exact test; p=0.034, one sided)

		Definitive Diagnosis		
		CRC	Benign & Normal study	Total
	Pilot sites not using e-RP	9	192	201
	e-RP referrals	25	246	271
	Total	**34**	**438**	**472**

Table 28 Yeild of e-RP for Colorectal Cancers

5.2 Delays In The Referral Process

Referral to first appointment

The time (median number of days) from referral to first appointment for CRC was 9 days (3-24) in the "Pilot Sites using e-RP" vs. 14 days (4-74) in patients referred from "Pilot Sites not using e-RP" (fig 12, table 29);

The right skewed data required log to the base 10 transformation before comparing means (log 10 mean 1.01vs. 1.20). The independent samples T test (t=–1.975, p=0.057, was borderline significant in this analysis.

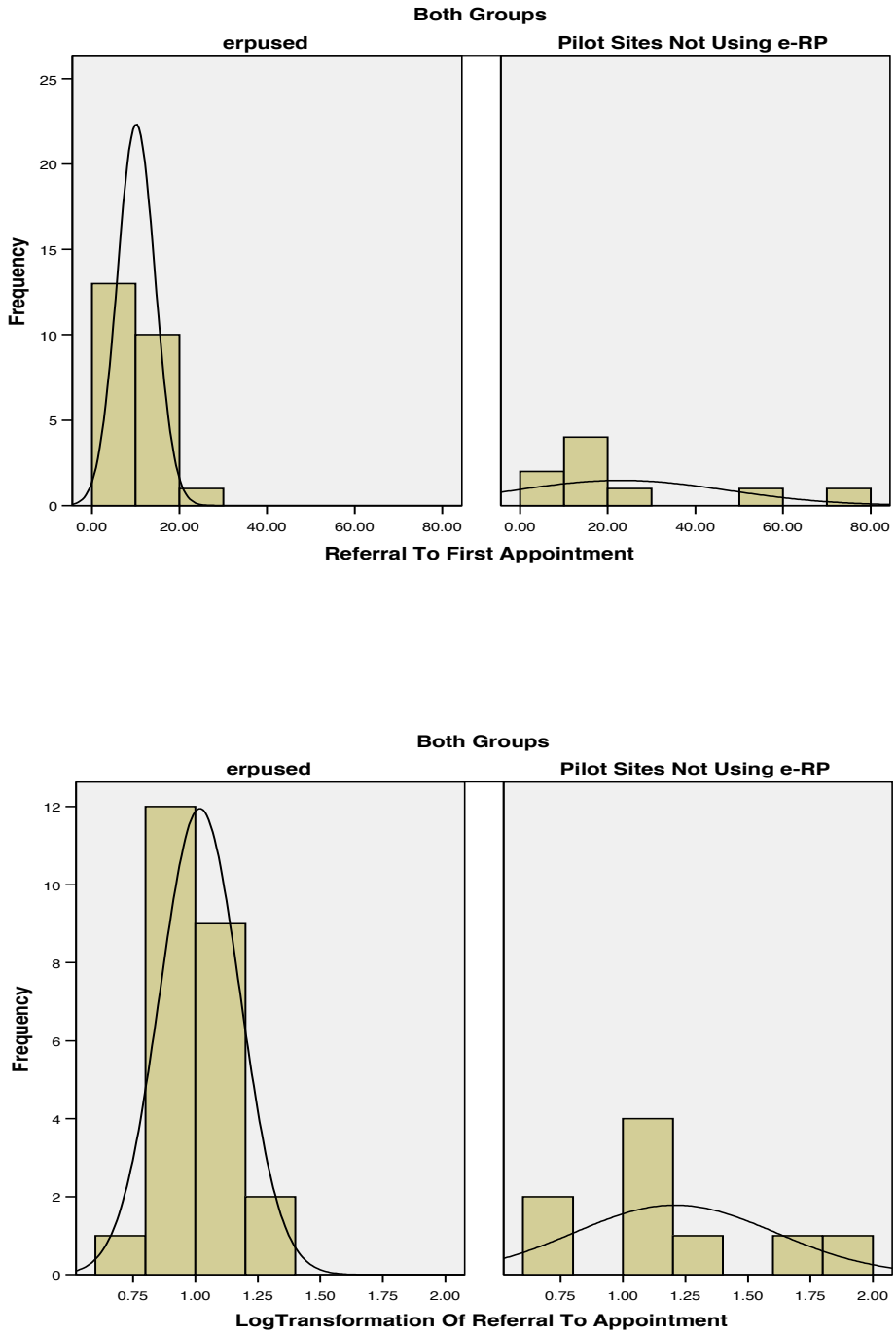


Figure 12 Referral to first appointment (days) for significant pathology and log 10 transformation for analysis.

Referral to First appointment				
Days	Mean	Median	Range	Missing
Pilot Sites using e-RP	10.12	9	3-24	1
Pilot Sites not using e-RP	23	14	4 to 74	0

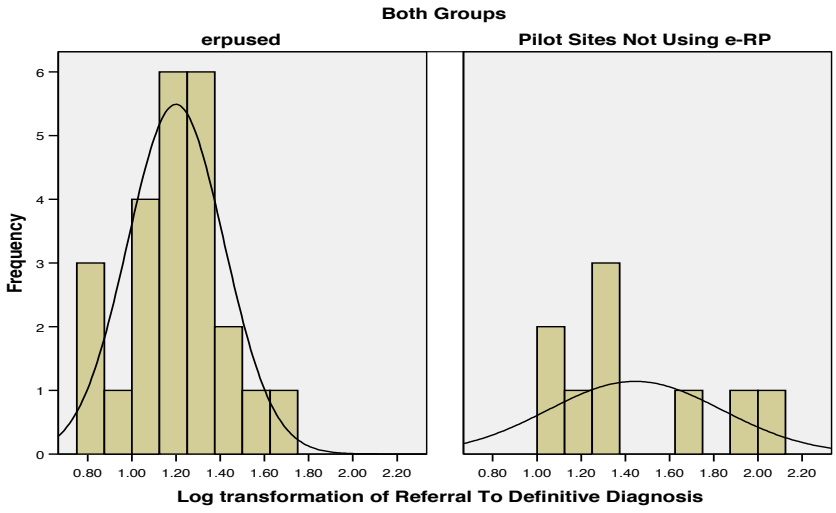
Table 29 Referal to first appointment (Pilot Sites using e-RP Vs. Pilot Sites not using e-RP).

The e-RP referrals eliminated “extreme delays” for first appointment, which were however, noted with the “Pilot Sites not using e-RP” for significant pathology.

Referral to definitive diagnosis

Median time from referral to definitive diagnosis for CRC was quicker in the “Pilot Sites using e-RP” (16 days: range 6 - 51) than in “Pilot Sites not using e-RP”(22 days: range 10-119) (fig 13, table 30). Due to the right skewed dataset, log to the base 10 transformations were carried out before comparing means (log 10 mean1.19 Vs log 10 mean 1.44).

Independent samples ‘T test’ revealed a significant reduction in delays to definitive diagnosis with the patients from “Pilot Sites using e-RP” (t= -2.284, p=0.029).



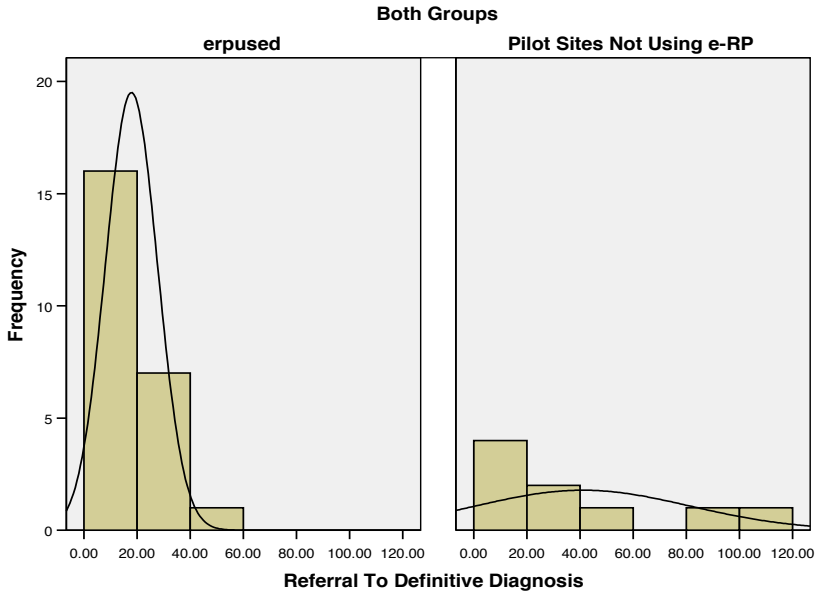


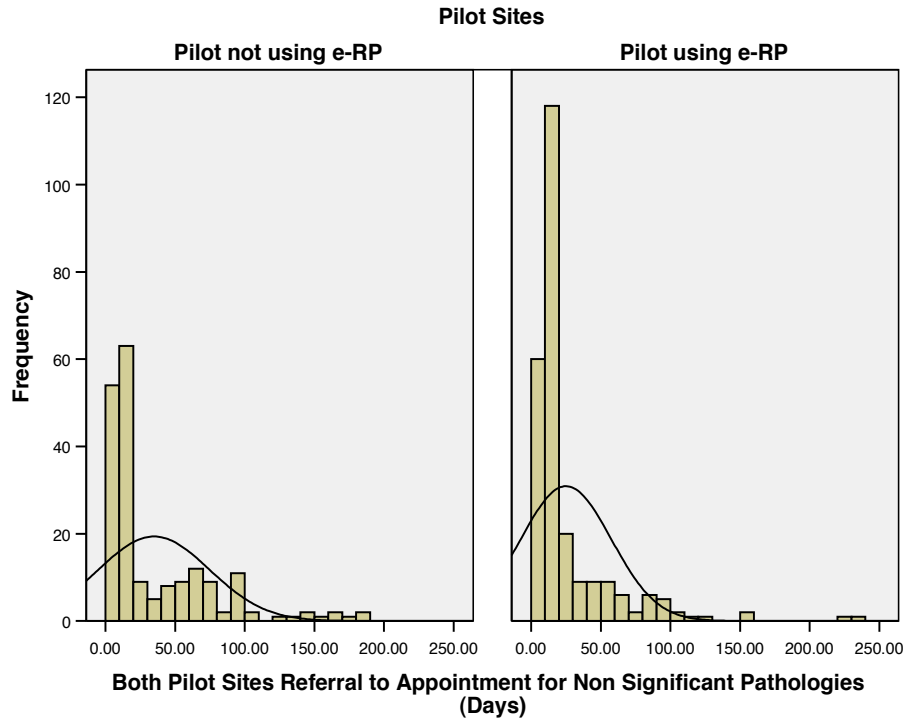
Figure 13 Referral to definitive diagnosis (days) for significant pathology and log 10 transformation for analysis.

Referral to Definitive Diagnosis				
Days	Mean	Median	Range	Missing
Pilot Sites using e- RP	17.8	16	6 to 51	1
Pilot Sites not using e-RP	41	22	10 to 119	0

Table 30 Referral to definitive diagnosis for CRC+>1cm polyps (Pilot Sites using e-RP vs. Pilot Sites not using e-RP)

Referral to first appointment for non-significant pathology

Patients diagnosed with non-significant pathology (not CRC), in the "Pilot Sites using e-RP" and "Pilot sites not using e-RP" were analysed to assess any differences.



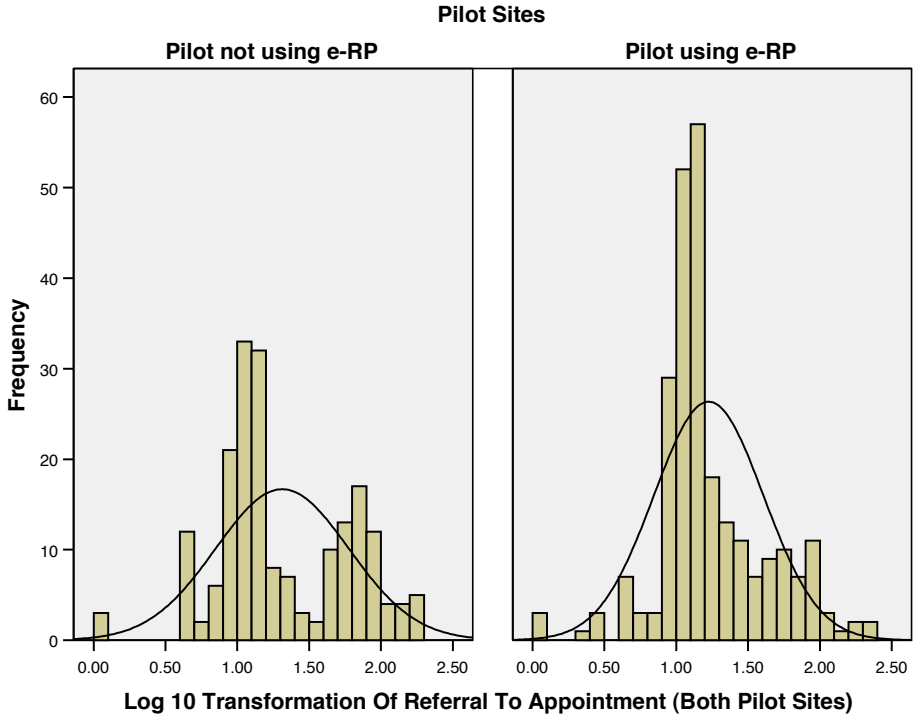


Figure 14 The referral to first appointment (days) for non-significant pathology and log 10 transformation for analysis

Median referral to first appointment, in the "Pilot Sites using e-RP" for non-significant pathologies was 13 days (range 0-237). This was not much different to "Pilot Sites not using e-RP", median of 14 days (range 3-182). However due to the right skewed datasets, log to base 10 transformation and analysis was carried out for more accuracy. There was

significant delay in “Pilot Sites not using e-RP”, mean 34.82 (log 10 mean 1.31) vs. 25.05 (log 10 mean 1.22) days, t-test 2.115, p=0.035, CI 0.00611 to 0.16769.

5.3 Straight to Test

Straight to Test was a function incorporated into the validated Lower Gastrointestinal e-Referral Protocol. The aim was to get patients with appropriate symptoms/signs to the correct destinations in secondary care as per local protocols. The following analysis looks at individual Straight to Test destinations; for example 'Straight to Colonoscopy' was compared for the "Pilot Sites using e-RP" vs. "Pilot Sites not using e-RP".

The specific points addressed were:

1) Total number of 'Straight to Test' referrals in both arms of the study.
2) The yield of significant pathology (CRC).
3) How appropriate is the location of the pathology, to the investigation used? (Right-sided pathology was designated as proximal to splenic flexure for this analysis).

Statistical analysis was carried out by Fisher exact test or Pearson's Chi-Square test as required, for each category of Straight to Test between the "Pilot Sites using e-RP Vs Pilot sites not using e-RP". Overall the patients were referred to various destinations in secondary care and the following tables give the proportion of patients in each destination as well as summarising the salient features of the analysis for all the modalities of 'Straight to Test' available in the Lower GI e-referral protocol. Out of 9 significant pathologies (CRC) from "Pilot Sites not using e-RP", 7 of them were redirected by consultants in secondary care to appropriate destination respectively. The analysis done below refers to comparisons after these amendments were made.

Straight to Colonoscopy

The e-RP was designed with the intention of detecting right-sided colonic lesions as Straight to Test with colonoscopy (table 31).

Straight to Colonoscopy	*Total*	*(%) Significant pathology*	*Appropriate Location of pathology*	*Comments*	*Statistics*
Pilot Sites using e-RP	29	16.6 (4incomplete I Cancelled)	4/4	All right-sided (4 CRC)	p-0.687 (Fisher exact)*
Pilot Sites not using e-RP	6	16.6	1	1Right Colon Cancer	

*Table 31 Straight to Colonoscopy. * Comparison between the e-RP arm and pilot sites not using e-RP.*

Straight to Rectal Bleed Clinic (Flexible Sigmoidoscopy)

The ability to pick up left-sided significant pathology with Straight to Flexible Sigmoidoscopy revealed a higher yield through the e-RP (table 32)

Straight to Flexible Sigmoidoscopy	*Total*	*% Significant pathology*	*Appropriate Location of pathology*	*Comments*	*Statistics*
Pilot Sites using e-RP	129	9.4 (5-incomplete 2 Cancelled, 5DNA)	10/11 One Caecal CRC)	10 left-sided CRC	p-0.27 (Chi square test)*
Pilot Sites not Using e-RP	66	5.6 (5 cancelled, 4DNA, 4Incomplete)	3/3	3 Left -sided CRC	

Table 32 Straight to Rectal Bleed Clinic (Flexible Sigmoidoscopy)

* Comparison between the e-RP arm and pilot sites not using e-RP.

Straight to Barium Enema

The GPs had the option to book patients for outpatient barium enemas through the e-RP, and this was analysed (table 33).

Straight to Barium Enema	*Total*	*% Significant pathology*	*Appropriate Location of pathology*	*Comments*	*Statistics*
Pilot Sites using e-RP	9	11.11	Yes (One caecal CRC)	5 Diverticular 3 Normal Outcomes	Overall small numbers prevent analysis
Pilot Sites not Using e-RP	2	50	One caecal CRC (Was palpable mass)	Could have been referred to Colorectal Clinic instead	

Table 33 Straight to Barium Enema

Straight to Colorectal Surgical Outpatient:

(Rigid Sigmoidoscopy + Clinical examination)

A higher yield of significant pathology was noted in the e-RP group, but a combination of right-sided and left-sided pathology was noted (table 34).

*Table 34 Straight to Colorectal Surgical Outpatients. * Comparison between the e-RP arm and pilot sites not using e-RP.*

Straight to Colorectal OPD	*Total*	*% Significant pathology*	*Comments*	*Statistics*
Pilot Sites using e-RP	98	16.6 (5 Incomplete, 2 DNA, 1 Cancelled)	Mixture of right and left-sided pathologies.	p-0.0001 Chi Square 14.45)*
Pilot Sites not Using e-RP	164	2.75 (9 cancelled, 5 DNA, 5 Incomplete)	2 CRC (rectal, right colon)	

Straight to Gastroenterology Outpatients

As expected, the yield of significant pathology through the gastroenterology outpatients was less compared to all other Straight to Test portals and this generally reflects the design of the e-RP to send benign non-surgical conditions to gastroenterology (table 35).

Pilot Sites	*Total*	*% significant pathology*	*Appropriate location of pathology*	*Comments*	*Statistics*
e-RP	85	7.79(8 incomplete)	Yes	No left sided CRC	p-1.0 Fisher's exact test*
Non e-RP	30	7.14 (2DNA)		2 left sided	

*Table 35 Straight to Gastroenterology Outpatients. * Comparison between the e-RP arm and pilot sites not using e-RP.*

5.4 Significant Pathology (CRC) As Two-Week-Wait Referrals

This section tries to answer the specific question as to whether e-RP can direct more cancers via the TWW route (Table 36). This analysis compares "Pilot Sites using e-RP" to "Pilot Sites not using e-RP".

	TWW	*Non-TWW*
Pilot Sites using e-RP	25	0
Pilot sites not using e-RP	6	2

Table 36 Pilot Sites using e-RP vs. Pilot Sites not using e-RP. One CRC patient excluded in the "Pilot Sites Not using e-RP" as Urgency of Referral unclear. p=0.014, Fisher's Exact test (2 sided)

5.5 Sensitivity and Specificity of e-RP In Directing Significant Pathology as TWW

This analysis was carried out for both groups (Pilot Sites not using e-RP and the Pilot Sites using e-RP). The sensitivity and specificity were calculated after excluding patients with incomplete episodes, DNAs and cancelled appointments. The proportion of excluded patients in the two groups was 12.2%, and 8% respectively.

The results derived (table 37) have to be considered with regard to the design of the trial, which imposes restrictions on the estimation of accurate overall denominators.

			Final Diagnosis		
			CRC	Other Benign and Normal Diagnosis	Total
Pilot sites not using e-RP	Priority	TWW	6	115	121
			75.0%	60.2%	60.8%
		Non TWW	2	76	78
			25.0%	39.8%	39.2%
	Total		8	191	199
			100.0%	100.0%	100.0%
e-RP referrals	Priority	TWW	25	172	197
			100.0%	70.2%	73.0%
		Non TWW	0	73	73
			.0%	29.8%	27.0%
	Total		25	245	270
			100.0%	100.0%	100.0%

Table 37 Sensitivity and Specificity of both routes for CRC (Sensitivity – shaded green and Specificity- shaded yellow). One CRC patient excluded in the "Pilot Sites Not using e-RP" as Urgency of Referral unclear.

5.6 Stage Changes

Looking at the colorectal cancer database for the Royal Bournemouth Hospital, overall Duke's (A & B) CRC predominated, 53% (2005-06) vs. 51% (2000-04).

A higher proportion of patients diagnosed with colorectal cancer through the e-RP route were Duke's stage A&B (48%) compared to "Pilot Sites not using e-RP"(35%); p=0.085, Chi Square 2.97, Yates corrected.

Due to the small sample size and low number of CRC diagnosed, any downstaging seen will be minimal in extent. However, a trend towards early stage disease was seen in the "Pilot Sites using e-RP".

6. Discussion

6.1 Summary of Results

This study has shown that the use of e-RP is associated with a statistically significant increase in yield of colorectal cancer diagnosis. There is statistically significant reduction in time to definitive diagnosis for colorectal cancer, plus a sensitivity of 100%, compared with 75% for non-use of e-RP. The patients diagnosed having colorectal cancer in the e-RP arm of the study, seem to have avoided extreme delays from GPs referral to first appointment in secondary care. There are several other changes which support the use of e-RP but which do not reach statistical significance, probably due to Type II error. I shall now go through the study in detail, examining strengths and weaknesses in the methods used, and starting with the validation study.

6.2 Discussion on Validation Study

The validation study has shown that application of the revised e-RP, which considers a wide range of colorectal symptoms, signs and history, would significantly increase the yield of colorectal cancers via the TWW route.

Lower gastrointestinal symptoms are common in the general population, and any mechanism to increase the effectiveness of the referral process from primary care must address the benign and less serious conditions as well as colorectal cancer. This has been demonstrated in various primary care studies, in which there was a significant overlap in symptoms in patients with colorectal cancer or benign conditions[88;141].

One of the commonest symptoms of colorectal cancer and other benign conditions is rectal bleeding, which is reported in 20 per cent of the general population in any one year[88]. Various studies in primary care have demonstrated significant colorectal diagnoses in between 20 and 45 per cent of those aged over 40 years presenting with rectal bleeding[89;145]. Another study of the primary care population aged between 18 and 75 years noted a colorectal cancer incidence of 3·3 per cent. In two recent prospective studies carried out in the UK, 3·4 per cent of those over 34 years presenting with rectal bleeding as the main symptom had colorectal cancer and all with colorectal cancer had an associated change in bowel habit[81].However, slightly different rates of 5·7 and 4·9 per cent were noted for colorectal cancer and colonic adenoma respectively in those older than 45 years presenting with rectal bleeding in a single general practice. This suggests that patients in the over 45 years group with rectal bleeding have a one in ten chance of having colorectal neoplasia, whether or not they have other symptoms[244].

Numerous studies in both primary and secondary care have analysed the ability of various combinations of highrisk symptoms and signs to pick up colorectal cancers, with varying degrees of success[50;78;79;82;83;89;107;109;141;143].

Although some of these studies have addressed the importance of specificity (true negatives that avoid investigation), the concept of improving sensitivity within the current service delivery provision should be considered.

The present validation study supports the latter as only 21 routine referrals were upgraded by the e-RP while picking up three colorectal cancers. Twenty-seven benign TWW referrals were reduced to less urgent categories but all cancers had TWW status. It has been well demonstrated in secondary care and recently in primary care that only 8–28 per cent of colorectal cancers present through the TWW route[229;245]. The revised version of the e-RP would lead to referral of 85·0 percent of colorectal cancers through the TWW route.

The concept of 'straight to test' speeds the diagnosis of patients within the TWW system[170]. The revised e-RP had some qualified success in this respect, as only seven patients with colorectal cancer would have been directed to a less appropriate test, due to grade of urgency assigned or tumour beyond reach of flexible sigmoidoscopy.

Selvachandran and colleagues[79] used a patient consultation questionnaire and a subjective weighted numerical score to prioritize patients seen in secondary care after referral from primary care. However, predominantly distal colorectal symptoms were assessed. The challenge for the e-RP is to address proximal colonic and distal colorectal symptoms, and clinical signs encompassing benign and malignant conditions, and to direct the patient to the most appropriate point of first contact, whether this be an investigation or the outpatient clinic.

Finally, the revised e-RP had the potential to reduce the rate of emergency presentation of colorectal cancers from 16·0 to 9·0 percent. This may demonstrate the value of a decision support system, the inference being that symptomatic patients are referred and investigated earlier, thus avoiding an acute admission. A recent retrospective study in primary care noted delays of up to 180 days before presentation in secondary care[61]. Two recent studies showed that 7 and 33 per cent of patients with colorectal cancer presented as emergencies in secondary care, even though formal elective referrals had already been made[139;245].

6.3 Design and Results of the e-RP Trial

The purpose of the trial was to identify the benefit of a validated revised e-RP at the primary care – secondary care interface specifically with regard to yield of CRC through the TWW system and appropriate referral destination in secondary care.
The objectives were achieved through the recruitment of general practitioners to use the e-RP on the 'Choose & Book' system. This chapter discusses the validity of these methods, and any biases that may have been introduced. It also discusses the conduct of the study, and any strengths and weaknesses resulting from this.

The parallel prospective design of this trial was the most pragmatic design, considering the various factors previously discussed in chapter 4. Randomisation either at general practice level (cluster) or individual GP was possibly the best design, but logistical difficulties were huge, in addition to higher number of general practices that would be required (~ 40 general practices in each arm).

There was also clear unwillingness from the GP's for individual GP randomisation. This was clear in the initial design stage of the trial when lead GP's were contacted. As I had previously discussed in chapter 2, there was significant intra general practice variability in the use and awareness of the TWW system, which in itself, could bias results. More over a GP sees approximately one patient with CRC/year and the relative rarity of this condition in itself will delay the overall duration and power of the study[191].

Design of the trial and conduct were modified post LREC suggestion. The issues mainly involved regarding consenting patients, i.e. where and when, to consent patient in the trial and how to minimize the dropout rate from the trial. However these issues were ironed out, by ensuring paperwork for consent was sent along with the appointment letter. This resulted in a higher than usual consent rate, which strengthened the study. The patients had ample time to go through the patient information leaflets and consent forms.
Easy access to the research team, helped many patients to clarify their doubts, even prior to their secondary care appointment.

The general practices, which took part in the trial, were those, which had accepted the invitation. They were allocated to intervention groups according to whether they accepted the first invitation or a subsequent one. Both arms were equally trained in use of e-RP, whether they used it over the trial period or not, and had the same educational input. This was in contrast to the non-pilot general practices, who did not accept an invitation to participate in the trial, did not receive training in use of e-RP and had no education input from the research team. There could be an argument, therefore, that this reduces the generalisability of the results, as participating practices, whether in the e-RP arm or not,

were more proactive and hence could be referring more patients with significant pathology. Similarly the GP's could be considered more knowledgeable than their counterparts in non-pilot general practices, as well as possibly more IT proficient. These arguments are difficult to prove or disprove, but clearly the general practices recruited to the pilot group, were a varied mix, looking at the variability in referral practice and use of the TWW referral system in the past (Chapter 2).

Alternatively, it might be that training both e-RP and non e-RP practices in the use of e-RP led to an element of contamination in the study, with practices acting according to the spirit of e-RP if not actually using e-RP itself. The alternative, however, would have been to compare the e-RP group with the non-pilot group, and this would clearly have been a biased comparison, with the obvious potential of volunteer bias. Given that we could not randomise, the comparison made is the correct one.

The age characteristics were very similar in all the three groups and this is unlikely to be a confounding factor in this study. Possibly the only noticeable difference (p-0.044) was between groups 1 (non-pilot sites) and 3 (pilot sites using e-RP) with mean age of 63.2 years and 65.5 years respectively. However, since this was not the main comparison in this study it is not relevant.

The CRC yield (excluding polyps>1cm) of 9.2% is much higher than 4.4% yield of CRC seen in another study[233]. It is possible the e-RP has been successful in picking CRC due to its characteristic of clustering symptoms and signs and possibility of lower threshold to refer patients with relevant symptoms for investigations. Various studies have previously quoted the benefit of clustering of symptoms both in primary care[78;81;82;84;96;141;145] and secondary care[50;78;79;142;143]. Moreover majority of CRC patient have a clustering of at least 3 symptoms & signs and this is possibly reflected in the e-RP arm of the trial[246]. The use of a validated decision support helps the GP to make a more appropriate referral to the right destination in secondary care.

Delays (in days) were calculated for significant pathology both from referral by GP to first appointment in secondary care and referral to definitive diagnosis. The former assess the GPs capability to assess patient and appropriately refer while the later address the delays to definitive diagnosis in secondary care and how important the concept of "Straight to Test" can be.

There has been lot published with regard to delays and influence on outcomes for individual patients diagnosed with CRC. The main issues are about patients becoming anxious, especially if symptoms had been present for months, if the GP had referred late,

and the patient was later diagnosed with CRC. This could potentially lead to litigation. Presentation at an advanced stage has been categorically linked to poor prognosis[247-251].

Looking at the results there was a clear tendency to "Eliminate Extreme Delays" in the "Pilot Sites using e-RP". Compared to a range of 21days in the "Pilot Sites using e-RP" for 'referral to appointment', the "Pilot Sites not using e-RP" had a range of 70 days for significant pathology. This kind of delay potentially could lead to more progressive disease and thus alter prognosis.

Similar findings are noted for 'referral to definitive diagnosis' as well. Range of 10-119 days in the "Pilot Sites not using e-RP" compared to 6-51 days in the "Pilot Sites using e-RP" for significant pathology. The e-RP has been successful by putting patients in appropriate clinical pathways early on the GP referral stage, avoiding all potential delays.

'Non significant pathology' also had similar delays when initially looked at, with a median of 13(0-237) days in "Pilot Sites using e-RP" & 14(3-182) days in "Pilot Sites not using e-RP". The right skewed datasets after transformation showed significant delay in the "Pilot Sites not using e-RP". This possibly could be explained by the combination of beneficial effect of e-RP to refer appropriately and early and slightly lower specificity, hence more referrals through the urgent or TWW route.

The concept of 'straight to test' evolved after extensive work done by the colorectal team at Leicester. They used the department of Health guidelines to design pathways for straight to investigation[170]. Previously only 62% of CRC were diagnosed in 31 days, but this improved to 100% after the new pathways were implemented in Leicester[170].

'Straight to test' was evaluated in this trial with an aim to direct patients appropriately to the right test /Outpatients. Location and yield of significant pathology was compared in the "Pilot Sites using e-RP" to the" Pilot Sites not using e-RP".

Percentage of significant pathology was higher in the "Pilot Sites using e-RP" only in the patients referred to colorectal outpatients clinic while yield were fairly similar in the other "straight to test" modalities. It is probably explained by the redirection of referrals with non-specific/benign symptoms to gastroenterology outpatients and specifically e-RP channelling patients referred with? 'Palpable mass or weight loss' to colorectal outpatients. This entirely fits with the previously mentioned increased yield of significant pathology through the e-RP.

The appropriateness of location of significant pathology (proximal or distal to splenic

flexure) was assessed and most of the e-RP pathways demonstrated the ability to deal with right sided and left sided symptoms/signs efficiently. No published work so far has looked into this aspect extensively as this trial has.

The patients destined to attend colorectal outpatients were those with palpable or suspicious abdominal/rectal masses, or those considered unfit for any diagnostics but requiring consultant input for management plans.

One of the endpoints in this thesis was to assess the ability of e-RP to direct more CRC as TWW. This has probably been the most prominent result in this trial with all 34 (100%) significant pathologies directed as TWW in the "Pilot Sites using e-RP". Pilot Sites not using e-RP referred only 13/15 referred as TWW, but this difference was non-significant. This finding could be possible due to the small numbers of CRC patients seen, requiring further validating in larger studies or could be considered as the benefit of a structured educational programme in primary care. This corresponds to only 30 (59%) being directed as TWW in the non-pilot sites.

The relevance of this is immense, as the fundamental concept of referral with DoH guidelines has failed to demonstrate similar results, and on average only a quarter of colorectal cancers referred to secondary care come through the TWW route[62;197;252].

The calculation of sensitivity & specificity in this study is limited by the study design, which imposes restriction on calculating the true denominators as many referrals would have to be ignored in the calculation due to lack of patient consent. Also referrals from only two PCTs were included in the study and this again limits the overall number of patients analysed. Hence a comparison with other studies published which have looked at sensitivity and specificity would be inappropriate[50;79;82;233;238]. These studies have used the whole patient population referred as denominators as they have been mostly carried out as audits studies rather than as a research projects.

The ultimate aim of any study looking at delays in CRC referral pathways, would like to see changes in the stage profile of these patients. This is probably the most relevant factor, which on an individual basis is most linked to prognosis and cancer specific survival[247-251].

Interestingly the cohort of CRC referred through the e-RP group had more Dukes' A & B stage patients than the "Pilot Sites not using e-RP" (48% Vs.35%), which was not statistically significant due to small numbers analysed. A study from Crew using a patient consultation questionnaire has published their work, which mentions a 30% Dukes A CRC

yield[112].

The overall Dukes' A+B disease was higher at 53% (2005-2006) compared to 51% (2000-2004). However this figure looks at the whole CRC work over two years and four years in this secondary care centre. This is different to the yield from the e-RP trial, as it corresponds to a period in 2006 predominantly and extending to early 2007.

6.4 Comparison with the Validation Study

Essentially the e-RP trial in primary care has more or less matched the outcomes from the validation study on two main aims of this thesis.

One is to direct patients with significant pathology as TWW referrals to secondary care. In the validation study, we have seen 85% of CRC were directed as TWW and 3 of the 4 CRC in the routinely referred cohort were upgraded to the TWW status. In the e-RP trial, interestingly 100% of patients with significant pathology were directed TWW. It is difficult to speculate the reasons for the better performance of e-RP in primary care setting in this regard, but could be possibly due to lower specificity of the e-RP in primary care setting, directing more referrals as TWW. The corollary was that the ratio of significant pathology to number of TWW referrals seen was best for the e-RP arm of the trial (1:4.8 Vs 1:8.6 in the non –pilot sites). Hence overall the effect of relatively lower specificity of e-RP in primary care setting is compensated by the higher yield of significant pathology with the e-RP.

The second aim of this thesis was to avoid extreme delays in patients with significant pathology and this seems to have been well handled by the e-RP by straight to test as appropriate and upgrading significant pathology as TWW.

The validation study proved the use of the revised e-RP in this regard and this was reflected in the trial.

6.5 Limitations and future applications of e-RP

This study involving the interface between primary and secondary care, has been a difficult but fruitful endeavour to arrive at certain conclusions, although for various reasons it has had its limitations.

The trial design and lack of randomization limits the usefulness of conclusions derived, but this study forms a platform to design larger trials in a more coordinated and randomized manner. Further strengthening of criteria to increase specificity e.g rectal bleeding in those over 50 years has resulted in higher number of patients through the two-week rule on the e-RP arm.

Similarly there is scope to analyze future data on a larger cohort, with respect to whether patients referred through the e-RP are a more elderly population?

The opposite speculation that might be a possibility is that the e-RP preferentially prevents younger patients (lesser probability of significant pathology) being referred and hence possibly altering referral practices. This speculation might be difficult to prove with this dataset, but something, which could be audited and compared few years later.

Future analysis for stage migration and influence on survival can be assessed at a later point for this cohort as well as future referrals coming in through the e-RP.

The effect of e-RP on health care economics is another potential area to explore.

7. Conclusion

This study has shown that a decision support algorithm, in the form of software, can offer significant support to GPs who come across one case of CRC in a year.

The project, with its various studies, has shed light on why rigid guidelines can fail and how actively educating GPs can have profound benefit. Currently only 57% of eligible patients accept the offer of screening, and some with positive faecal occult blood tests decline further investigations. These two factors taken together, means that only around a quarter of colorectal cancer patients will be identified by screening currently. This is however likely to change as proportion of screen detected CRC increases and the benefit of e-RP will be for the slowly dimishing percentage of symptomatic CRC. General Practitioners familiarity and the initial process of active and passive learning by using the e-RP, would however lead to lesser use of the e-RP in the long run as demonstrated in previous studies on decision support devices.

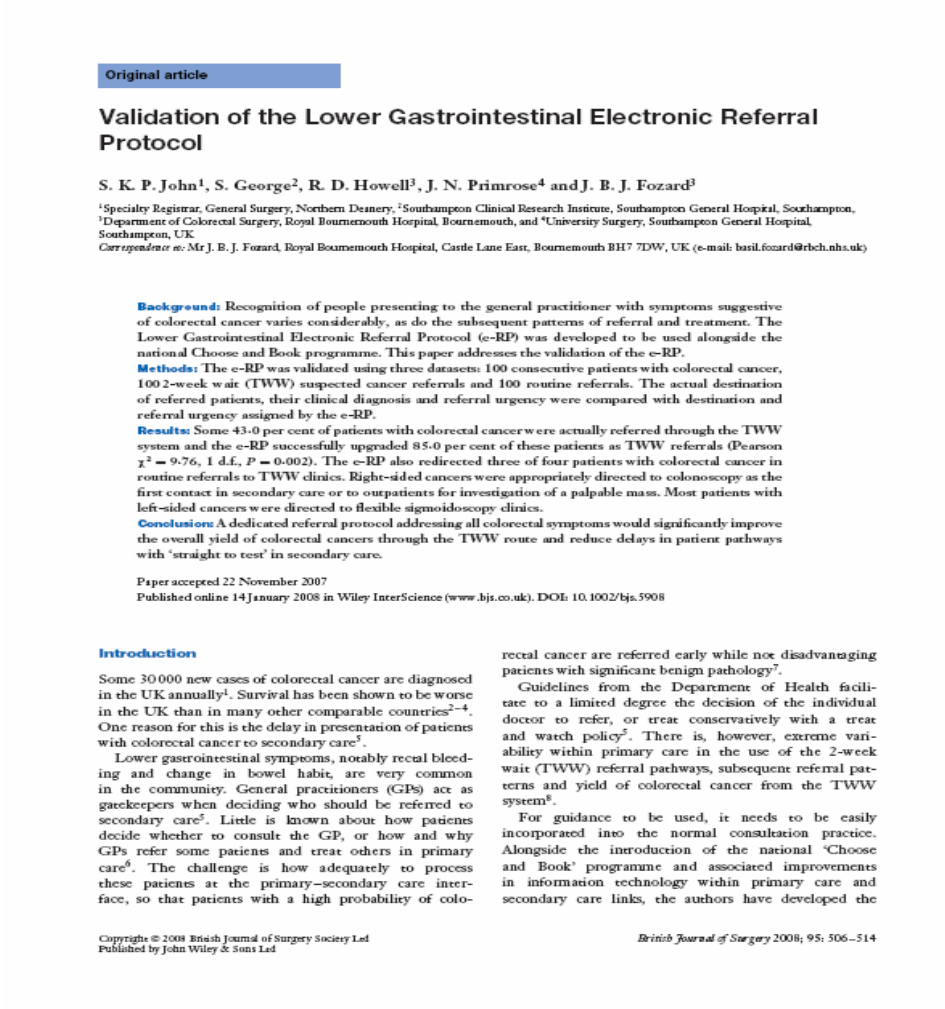
This study lays the foundation for larger/different population studies to help validate these results further. Measures such as e-RP can ultimately pick early CRC and may provide survival advantage in the longer run.

Appendix A

Publications of relevance to this project

Original Papers

1. Validation of theLower Gastrointestinal Electronic Referral Protocol; John SKP, George S, Howell RD, Primrose JN, Fozard JBJ. British Journal of Surgery; 2008; 95:506-514



Original article

Validation of the Lower Gastrointestinal Electronic Referral Protocol

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Background: Recognition of people presenting to the general practitioner with symptoms suggestive of colorectal cancer varies considerably, as do the subsequent patterns of referral and treatment. The Lower Gastrointestinal Electronic Referral Protocol (e-RP) was developed to be used alongside the national Choose and Book programme. This paper addresses the validation of the e-RP.

Methods: The e-RP was validated using three datasets: 100 consecutive patients with colorectal cancer, 100 2-week wait (TWW) suspected cancer referrals and 100 routine referrals. The actual destination of referred patients, their clinical diagnosis and referral urgency were compared with destination and referral urgency assigned by the e-RP.

Results: Some 43·0 per cent of patients with colorectal cancer were actually referred through the TWW system and the e-RP successfully upgraded 85·0 per cent of these patients as TWW referrals (Pearson $\chi^2 = 9{\cdot}76$, 1 d.f., $P = 0{\cdot}002$). The e-RP also redirected three of four patients with colorectal cancer in routine referrals to TWW clinics. Right-sided cancers were appropriately directed to colonoscopy as the first contact in secondary care or to outpatients for investigation of a palpable mass. Most patients with left-sided cancers were directed to flexible sigmoidoscopy clinics.

Conclusion: A dedicated referral protocol addressing all colorectal symptoms would significantly improve the overall yield of colorectal cancers through the TWW route and reduce delays in patient pathways with 'straight to test' in secondary care.

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Introduction

Some 30 000 new cases of colorectal cancer are diagnosed in the UK annually[1]. Survival has been shown to be worse in the UK than in many other comparable countries[2–4]. One reason for this is the delay in presentation of patients with colorectal cancer to secondary care[5].

Lower gastrointestinal symptoms, notably rectal bleeding and change in bowel habit, are very common in the community. General practitioners (GPs) act as gatekeepers when deciding who should be referred to secondary care[5]. Little is known about how patients decide whether to consult the GP, or how and why GPs refer some patients and treat others in primary care[6]. The challenge is how adequately to process these patients at the primary–secondary care interface, so that patients with a high probability of colorectal cancer are referred early while not disadvantaging patients with significant benign pathology[7].

Guidelines from the Department of Health facilitate to a limited degree the decision of the individual doctor to refer, or treat conservatively with a treat and watch policy[5]. There is, however, extreme variability within primary care in the use of the 2-week wait (TWW) referral pathways, subsequent referral patterns and yield of colorectal cancer from the TWW system[8].

For guidance to be used, it needs to be easily incorporated into the normal consultation practice. Alongside the introduction of the national 'Choose and Book' programme and associated improvements in information technology within primary care and secondary care links, the authors have developed the

2. Inter General Practice Variability in Use of Referral Guidelines for Colorectal Cancer; John SKP, Jones OM, Horseman N, Thomas P, Howell RD, Fozard JBJ; Colorectal Disease, 2007; 9: 731-735.

Original article

doi:10.1111/j.1463-1318.2006.01201.x

Inter general practice variability in use of referral guidelines for colorectal cancer

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Abstract

Objective The Two-Week Wait (TWW) referral system for suspected colorectal cancers has a low yield. To examine this, we assessed the referral pattern of general practices within their primary care trusts and looked at the variability of yield of colorectal cancer amongst all TWW referrals and assessed the reasons for variability.

Method A prospectively collected database of all colorectal cancers was examined for new cases diagnosed in the 12 months from April 1st 2004. Patients were cross-referenced via general practitioner (GP) codes to identify the referral origin. Reasons for the variability in referral patterns from each general practice were assessed in relation to TWW referrals, population demographics and through postal questionnaire of GPs.

Results A total of 175 patients diagnosed with colorectal cancer were referred from 49 general practices. Whilst there was a positive correlation between the number of TWW referrals and colorectal cancer per 1000-practice population ($P = 0.001$; Spearman correlation coefficient $r_{s,48,two\text{-}tailed}$, two-tailed), there was a big discrepancy between referrals and cancer diagnosed in many general practices. Twenty-six general practices (53%) had no colorectal cancer diagnosed via the TWW route and these practices had significantly lower utilization of the TWW referral pathway. In the postal survey, 22% of GPs were unaware of TWW clinics or colorectal cancer referral guidelines and only 8% of GPs knew the number of referral criteria.

Conclusion This study demonstrates wide variability within primary care, in the appropriate use of colorectal cancer referral guidelines. General practices should be targeted for education.

Keywords Colorectal cancer, Two-Week Wait Referrals, general practice, general practitioner, guidelines

Introduction

Colorectal cancer referral guidelines and Two-Week Wait (TWW) clinics for suspected colorectal cancer were introduced in July 2000 [1,2]. However, this pathway for referral to secondary care is often used inappropriately [3–8]. It has been suggested that this reflects poor referral guidelines [6,7] and their inappropriate use by general practitioners (GPs) [5,9].

The current study aims to assess the pattern of referral behind the current low yield of colorectal cancer from the TWW referral system. The influence of other factors including general practitioner age, educational input and population demographics was explored.

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Method

From a prospectively recorded database of all colorectal cancers, we carried out data extraction for a period of 1 year from April 2004 to March 2005, utilizing GP codes against each colorectal cancer diagnosed. We derived further data from the database, assessing the number of TWW referrals made in the same time period. The total number of cases with colorectal cancer, the route of referral and the number of TWW referrals were then analysed for each GP code and also individual general practices. Forty-nine general practices within four Primary Care Trusts (PCTs) were involved in the study.

Primary Care Trusts provided data on the population of each general practice and the subgroup of patients aged 60 years and above. The educational needs of GPs and their awareness of colorectal referral guidelines were

3. Symptoms and signs in patients with colorectal cancer, A review; **John SKP**, George S, Primrose JN, Fozard JBJ. **Colorectal Disease; 2010**; 13, 17-25

Review article

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Symptoms and signs in patients with colorectal cancer

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Abstract

The symptoms and signs of colorectal cancer vary from the general population to primary care and in the referred population to secondary care. This review aims to address the diverse symptoms, signs and combinations with relevance to colorectal cancer at various points in the diagnostic pathway and tries to shed light on this complex and confusing area. A move towards a lower threshold for referral and increased use of diagnostics might be a more reliable option for early diagnosis.

Keywords Colon cancer, rectal cancer, rectal bleeding, anaemia, change in bowel habit

Introduction

The National Bowel Cancer Screening Programme aims to reduce the incidence of symptomatic colorectal cancers (CRC); however, the overwhelming majority of patients present to their general practitioner (GP) with symptoms [1–3]. Surgical emergencies, principally obstruction or perforation in 3–31% of hospital series comprise the rest, with UK figures among the highest in comparable economies [2,4–8].

Although many symptoms are associated with CRC, few are unique. Symptoms and signs can occur in isolation or more commonly as clusters, and almost 85% of CRC patients referred to secondary care have one or more high-risk symptoms [9].

Observations on the predictive value of symptoms for disease can be seriously biased by 'selection phenomena', and this is applicable to CRC [10]. Selection bias may occur at the general population level with consultation behaviour in primary care or after referral to secondary care. This bias is often ignored when carrying out diagnostic research in secondary care [11]. Moreover, the primary symptoms of bowel cancer in the primary care setting may be quite different to those in the community and in hospital practice [10]. To devise any algorithms for CRC, probability in primary care and subsequent referral to secondary care [12], the positive predictive value (PPV) for each symptom or sign alone and/or in combination is often considered useful [11,13]. There are gaps in the current published reports on incidence, prevalence and PPV estimates for the whole spectrum of colorectal symptoms and signs. This overview attempts to address some of those gaps.

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Method

We searched for studies assessing the accuracy of symptoms presenting in primary care in predicting the diagnosis of CRC. Ovid Medline (1950 to early 2009) and Embase (1980 onwards) searches were carried out using the 'MESH' and 'Non MESH' terms of 'rectal bleeding', 'diarrhoea', 'weight loss', 'abdominal pain', 'constipation', 'anaemia', 'colorectal cancer', 'family history' combined with 'population studies', 'primary care', 'general practice' and 'hospital studies' as keywords. Only published English-language studies were included because of resources for translation. We used eventual diagnosis of CRC as the reference standard.

Data collection and analysis: selection of studies

A list of articles meeting the inclusion criteria based on abstracts was compiled. These and those of uncertain relevance were retrieved in full text. Two reviewers independently evaluated each group of studies for inclusion, with any discrepancies being discussed with a third reviewer until a final set of relevant studies was agreed. The methodological quality for each article was assessed

Abstarcts

1."More CRC, More A&B, Results from a Prospective Trial of Decision Support in Primary Care". BJS 2008; 95 (S3), p 75-76.

2. Decision support pathway in "choose and book" for colorectal referrals-a way forward- BJS 2007; 94(S2): 38

3. Targeted education and option to use a Decision Support Protocol (DSP) within primary care-Possible solution to earlier diagnosis of colorectal cancer. BJS 2007; 94(S2): 38

4. Inter general practice variability in referral of patients suspected of having colorectal cancer- a Hugh education gap. BJS 2007; 94(S2): 38

5.'Lower GI electronic referral protocol'. Analysis of 300 referral episodes - BJS 2006 Supplement, Vol 93, 05/2006.

6.Inter general practice variability in referral of patients suspected of having colorectal cancer- a Hugh education gap. Colorectal Disease, Supplement 2, 2007; Vol 9

Appendix B

Useful correspondence and teaching templates of e-RP

The Royal Bournemouth and Christchurch NHS Foundation Trust

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UnitedKingdom
http://www.rbch.nhs.uk
20th April 2006

Dear Colleague

We are in the process of conducting a survey looking at "Interpractice Variability Of Use Of Colorectal Referral Guidelines". The survey will be useful in assessing patterns of referral from primary care and any significant variability in use of colorectal referral guidelines.

I should be grateful if you will complete the single page questionnaire and return it in the post paid envelop attached.
The results of this survey will be totally anonymous and we will provide individual practice based feed – back. Please find enclosed your current colorectal fast-track referral pattern compared to other practices.

With kind regards.
Yours sincerely
Mr JBJ Fozard,

COLORECTAL CANCER LEAD &
CLINICAL DIRECTOR, SURGERY

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JBF/jr 02-06
9th February 2006
Dear Colleague

We are in the process of conducting a pilot study of a decision support system for lower GI referral within the context of Choose & Book.
I am sure that the Choose & Book system is still causing some difficulties, but the decision support system adds around thirty-seconds/one minute to the process of referral.
I should be very grateful for the opportunity to come and discuss this with you either individually or on a Practice basis. If you are interested, then please contact my Research Fellow, Mr Solomon John, Solomon.John@rbch.nhs.uk, RBH, Post Point. D52, Tel: 01202 704080 or mobile 07791519726, and we can agree a mutually convenient time. The process would take approximately 30 minutes to explain.

With kind regards.

Yours sincerely

Mr JBJ Fozard
CLINICAL DIRECTOR, SURGERY
c.c. Solomon John, Research Fellow, RBH

Department Of Colorectal Surgery

Study on "Lower Gastrointestinal e-Referral protocol"

Dear Dr. Gamper,

We thank you for inviting us to come and discuss about the project. The project started from February 2006. Please feel free to use the protocol whenever referring patients to colorectal surgery, gastroenterology and endoscopy services.

Some of the symptom pathways are simple two-step pathways (especially when dealing with high risk colorectal cancer symptoms) while low risk symptom pathways would have more steps for categorising severity.

The success of the study would depend on consistent use of protocol either going with the decision support or overriding, either way we would audit outcomes and refine the protocol further if need be.

A detailed "Utility guide " for the use of the "Lower GI e-Referral Protocol" has been provided with this letter. If you need any further information on any matter to do with this project, please get in touch with Mr.Solomon John,
Research Registrar, Colorectal surgery.
I once again thank you for your interest and support for this study.
Yours truly,
Mr.J.B.J.Fozard,
Consultant Surgeon
Colorectal Cancer Lead,
Chief Investigator

Contact details
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Lower Gastrointestinal e-Referral Protocol Study

(Non- randomised clinical trial on use of a dedicated referral pathway in primary care to secondary care for colorectal symptoms and suspected anaemia)

Main Study:

14 General Practices in Bournemouth Primary Care Trust

Utility Guide

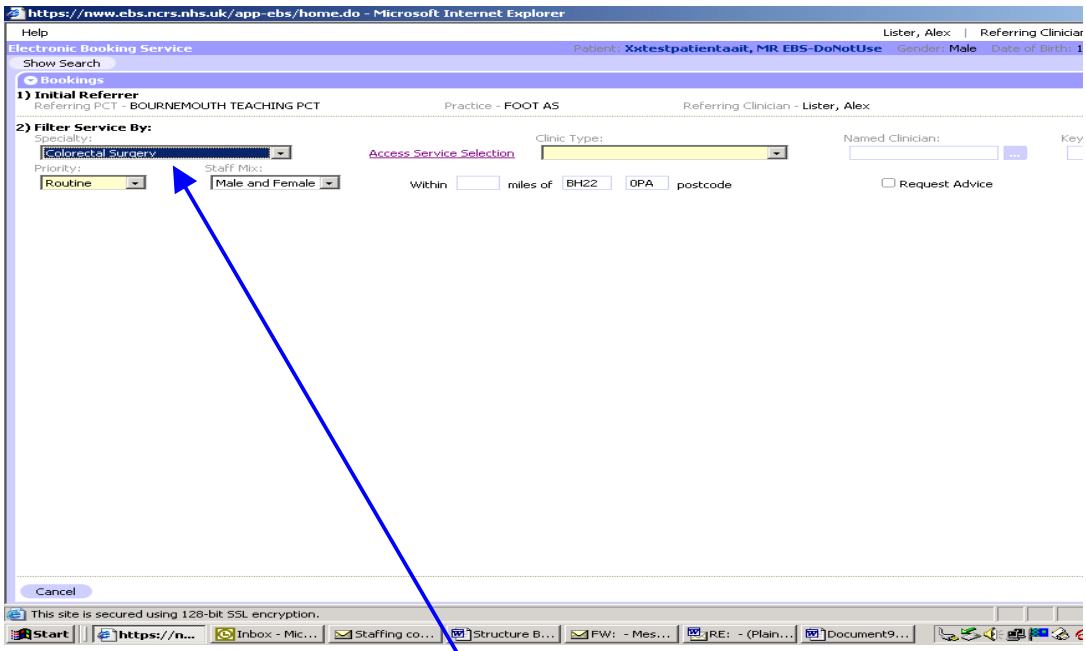
1. The e-Referral protocol is on Choose and Book program.

2. This essentially means using the "e-Referral protocol" only when you feel the patient needs referral to Royal Bournemouth Hospital.

3. Criteria for referrals to be included in the study:

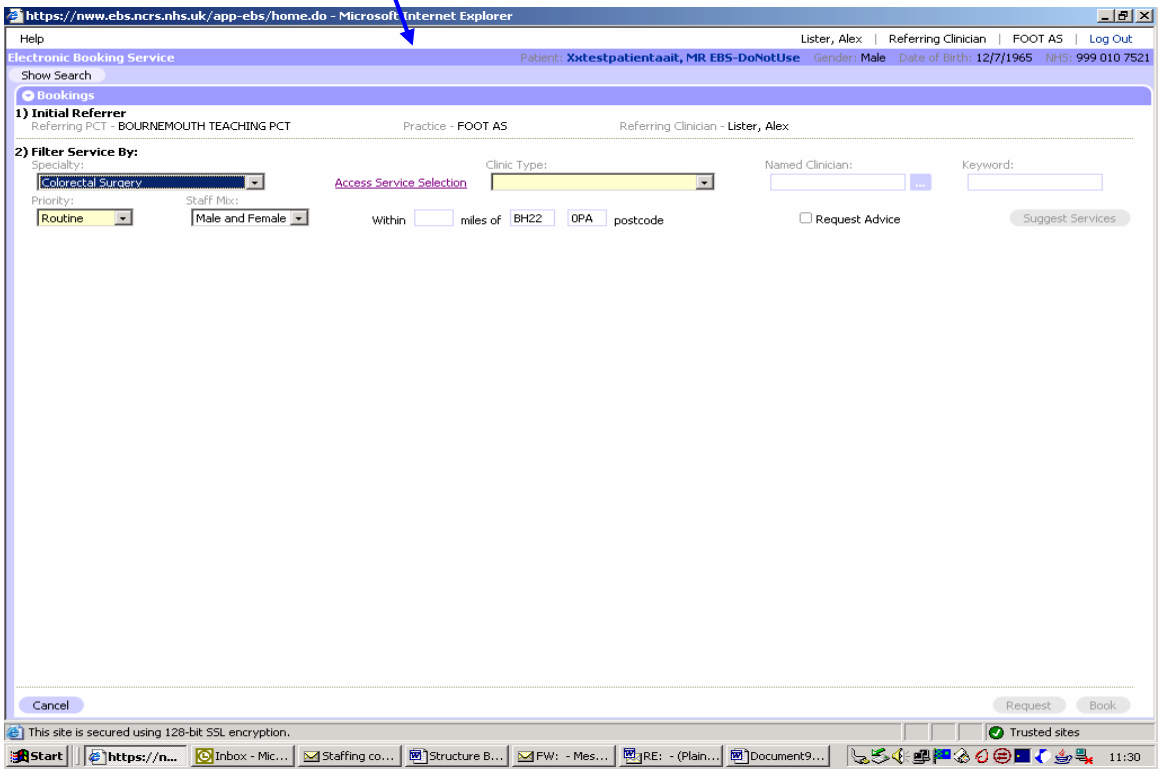
    a) Adults (>18 years) referred with colorectal symptoms for the first time to secondary care.
    b) Adults (>18 years) with possible iron deficiency anaemia for evaluation (Haemoglobin <13 gm% in males and <12 gm% in females).

4. After logging on Choose and Book ⟶ Go to the referral page



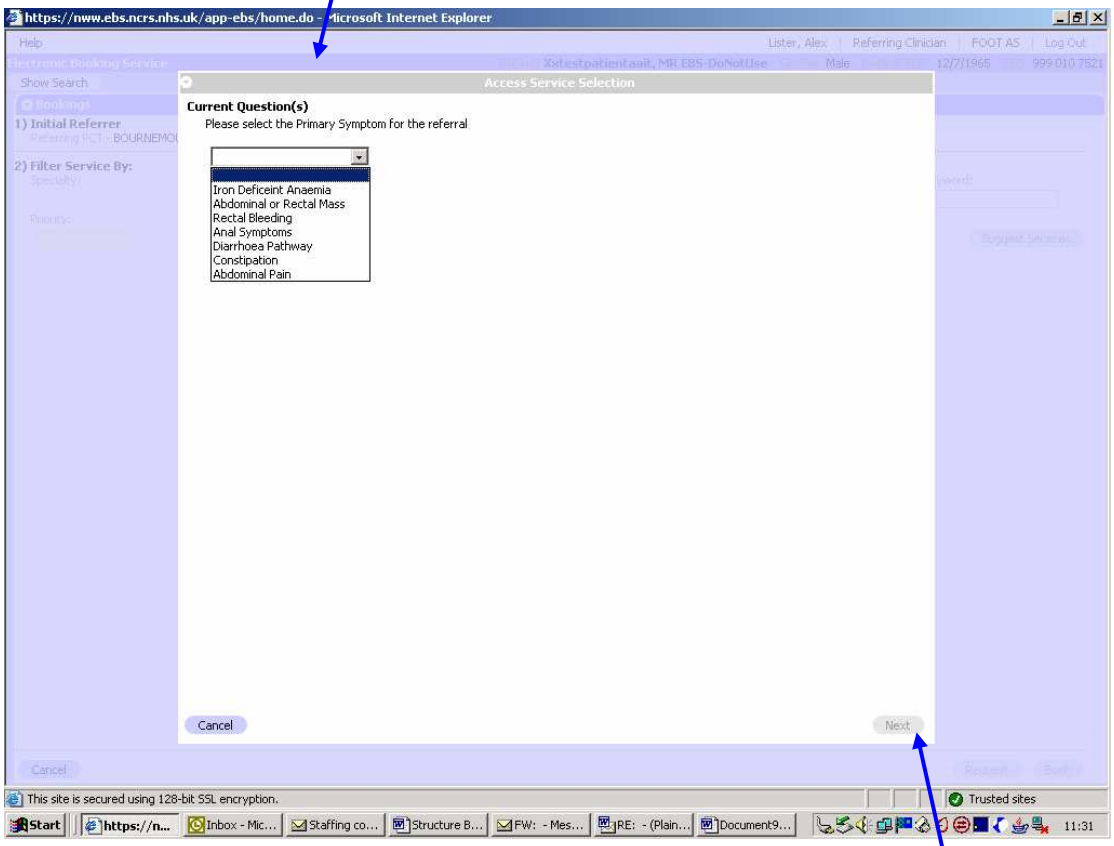
Go to "Colorectal Surgery" or "Gastroenterology"

5. Use “Access Service Selection”



The “Access Service Selection” is only active for **Colorectal Surgery and Gastroenterology in Bournemouth PCT**. The location of the “e-Referral protocol” on choose and book has to be confidential to the pilot general practices. Further modifications and upgrades on the “e-Referral protocol” will be based on results from pilot study.

6. Takes us to **“Lower GI e-Referral Protocol” (Primary Symptom Page)**

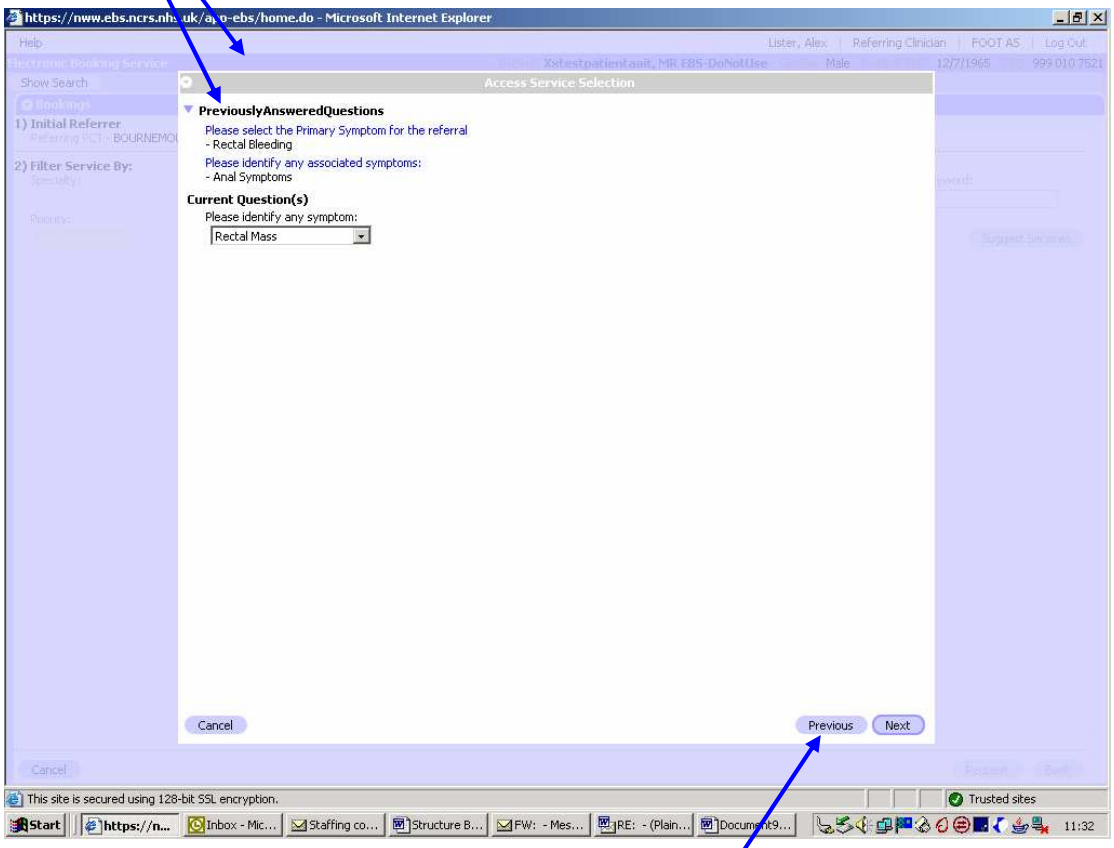


Click Next

Please use the main symptom you feel the patient has or is clinically significant to enter the “e-Referral protocol”. Further questions would assess the associated symptoms of relevance if any and give urgency and destination of referral.

7. Can go back to previous questions by two routes:

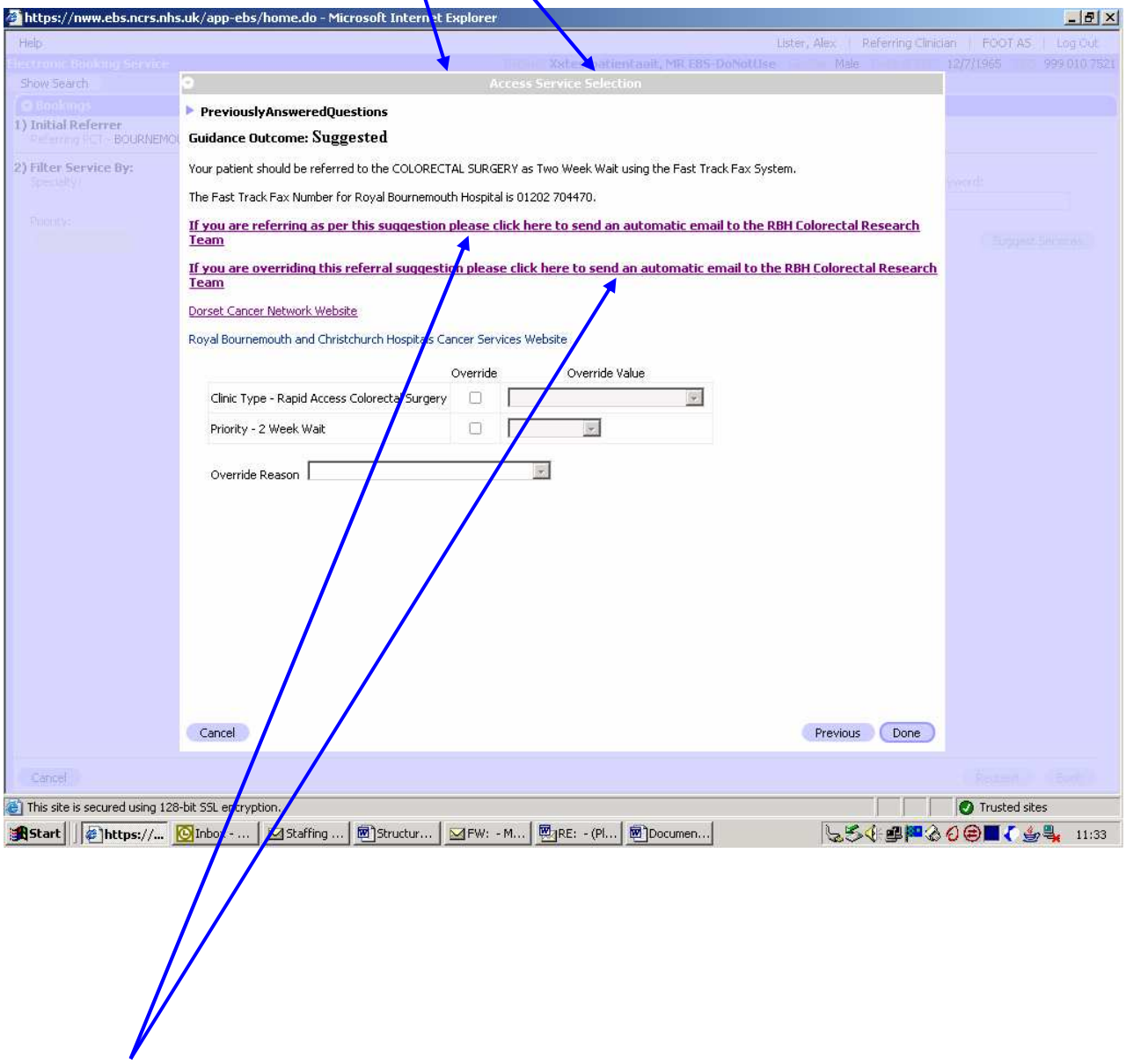
Click Here



Or Click Here

Outcome Page 1

(1) Protocol assigned outcome

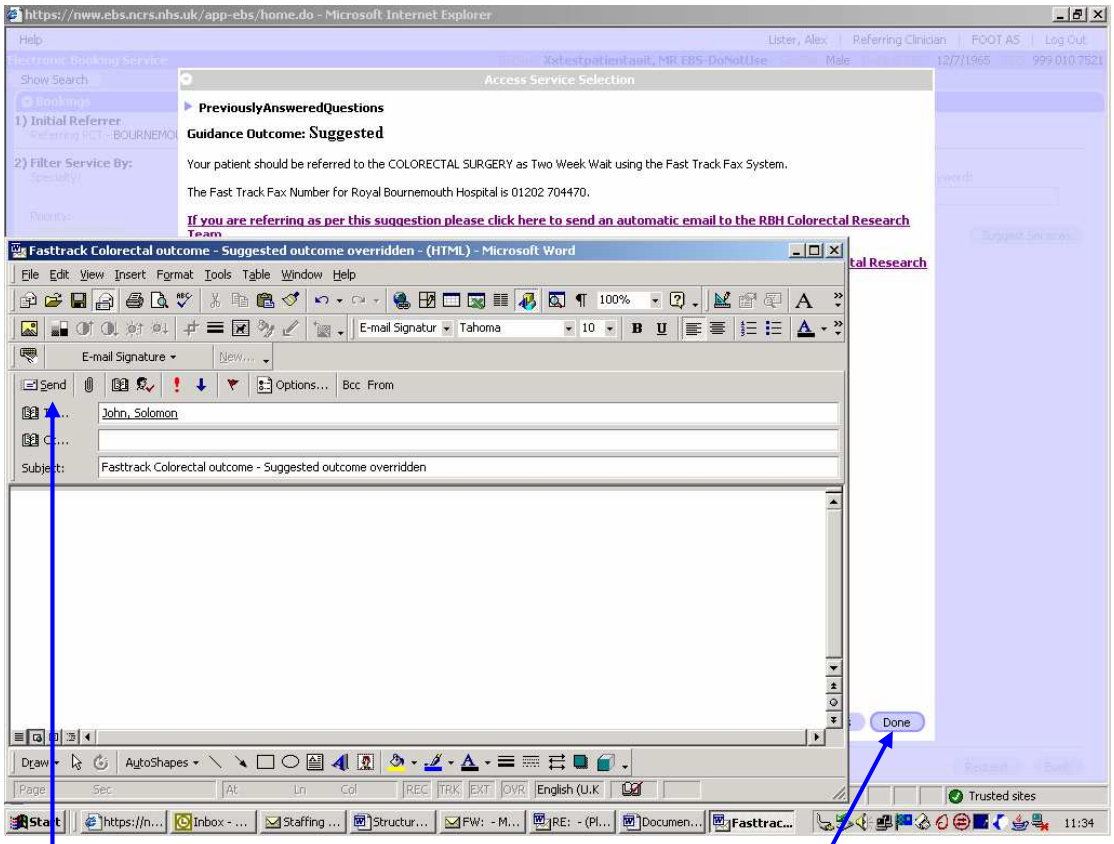


(2) Please Click on either link as per your decision matching or overriding of "e-Referral protocol". We need to know you have used the "e-Referral protocol" to audit the protocol and refine it.

ATTENTION

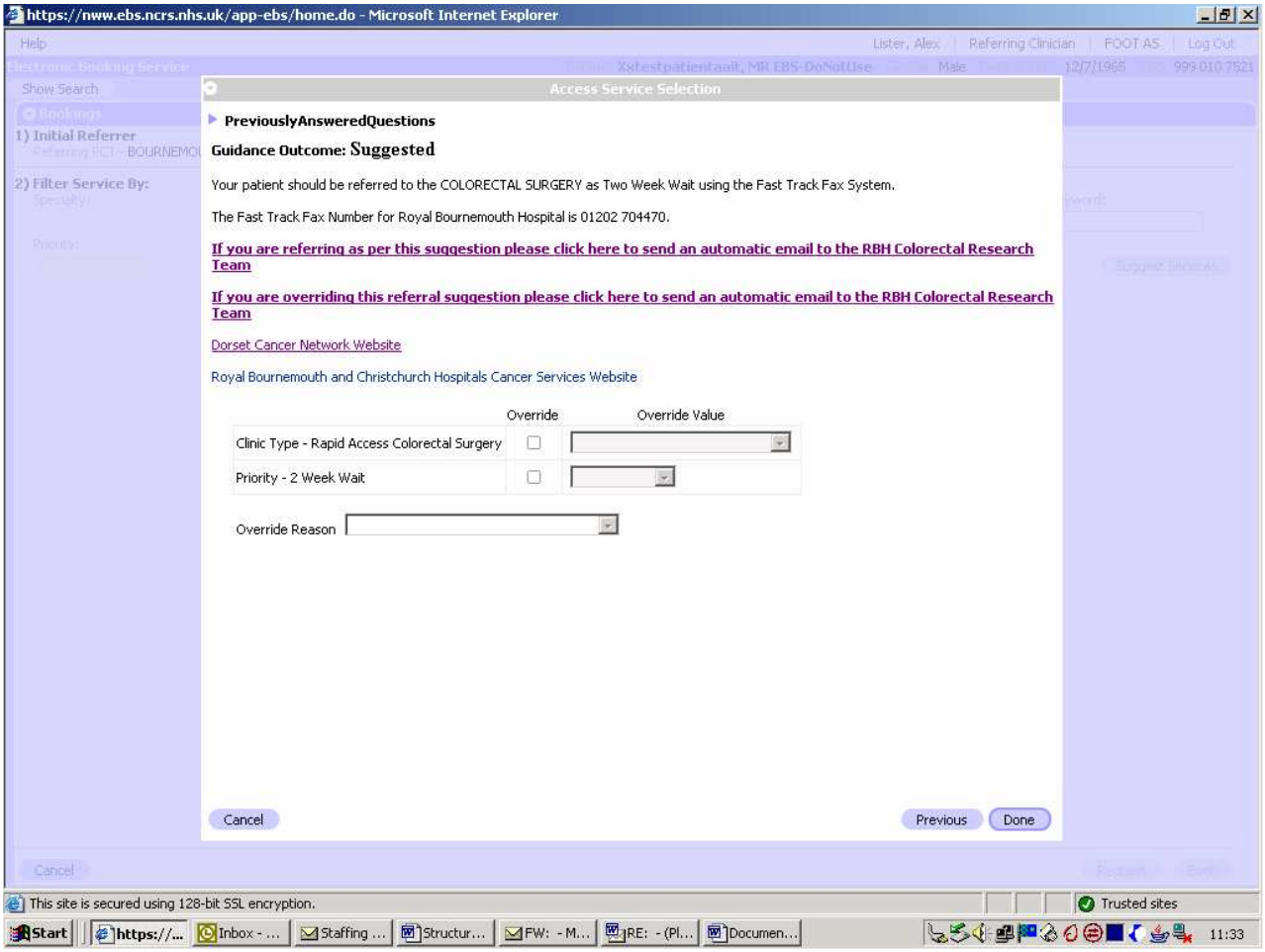
For Fast-Track Outcome: Please Fax To: 01202 704470

Outcome Page 2



Send e-mail (Please enter patient name and hospital ID)

Click Done (takes you to referral page on choose and book)


https://nww.ebs.ncrs.nhs.uk/app-ebs/home.do - Microsoft Internet Explorer
Help
Lister, Alex | Referring Clinician | FOOT AS | Log Out
Electronic Booking Service
Show Search
Bookings
1) Initial Referrer
2) Filter Service By:
Access Service Selection
PreviouslyAnsweredQuestions
Guidance Outcome: Suggested
Your patient should be referred to the COLORECTAL SURGERY as Two Week Wait using the Fast Track Fax System.
The Fast Track Fax Number for Royal Bournemouth Hospital is 01202 704470.
If you are referring as per this suggestion please click here to send an automatic email to the RBH Colorectal Research Team
If you are overriding this referral suggestion please click here to send an automatic email to the RBH Colorectal Research Team
Dorset Cancer Network Website
Royal Bournemouth and Christchurch Hospitals Cancer Services Website
Override
Override Value
Clinic Type - Rapid Access Colorectal Surgery
Priority - 2 Week Wait
Override Reason
Cancel
Previous
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This site is secured using 128-bit SSL encryption.
Trusted sites
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Lower Gastrointestinal e-Referral Protocol Study

(Non- randomised clinical trial on use of a dedicated referral pathway in primary care to secondary care for colorectal symptoms and suspected anaemia)

Main Study:

14 General Practices in Bournemouth Primary Care Trust and Practices in S.E.Dorset PCT.

Utility Guide

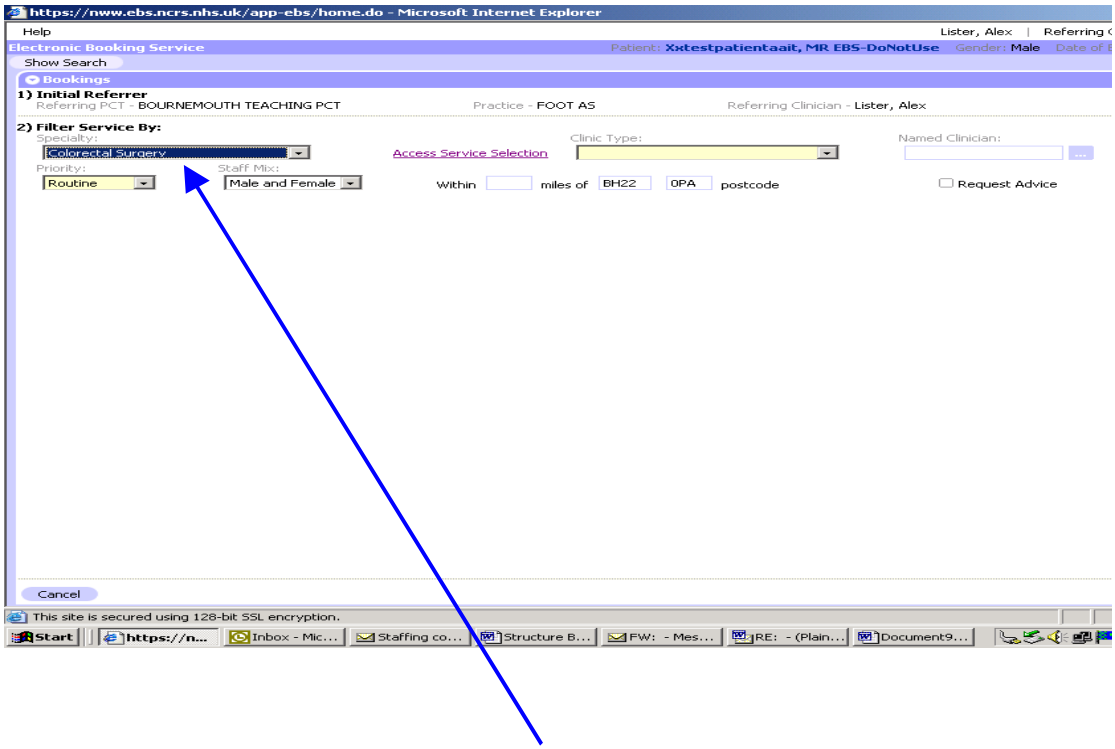
1. The e-Referral protocol is on Choose and Book program.

2. This essentially means using the "e-Referral protocol" only when you feel the patient needs referral to Royal Bournemouth Hospital.

3. Criteria for referrals to be included in the study:

    a) Adults (>18 years) referred with colorectal symptoms for the first time to secondary care.
    b) Adults (>18 years) with possible iron deficiency anaemia for evaluation (Haemoglobin <13 gm% in males and <12 gm% in females).

4. After logging on Choose and Book ⟶ Go to the referral page



The Royal Bournemouth and Christchurch Hospitals

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Department of Colorectal Surgery

Evaluation of Lower Gastrointestinal e-referral Protocol

PATIENT INFORMATION SHEET

The Study to analyse effectiveness of an electronic protocol for referring patients with bowel symptoms or low blood count (anaemia) to the Hospital.

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully .You could discuss with your GP if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

What is the purpose of the study?

The department is constantly striving to improve the efficiency in the referral process. We wish to find out if an electronic referral method from your GP surgery to the hospital could be designed and used. This electronic referral method could be used by your GP, applying your specific symptoms and assessing the need to refer you to The Royal Bournemouth Hospital or not.

This method would also assign adequate and appropriate urgency to your symptoms and help your GP to refer you to the hospital to the correct department at the right speed.

Why have I been chosen?

You have been chosen because you are above 18 years, referred by your GP to one of the following Surgeons or Gastrointestinal Doctors at The Royal Bournemouth Hospital due to bowel symptoms or low blood count (anaemia).

Surgeons:

Mr J.B.Fozard

Mr R.J.Lawrance

Mr.R.Howell

Gastrointestinal Doctors:

Dr.P.J.Winwood

Dr.R.M.McCrudden

Dr.S.Weaver

Dr.J.Ainley

Do I have to take part?

It is up to you to decide whether or not to take part. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive. If for any reason, you were found to be unsuitable for the study, please rest assured that your treatment or investigations would not be affected at all.

What would happen to me if I take part?

You would have an outpatient appointment as usual in a normal manner. If you give us your consent, your data would be used in our study. We would look into time periods you experience, for example between referral and first appointment. The outcome of any tests you may have would also be recorded. All this information would be totally anonymous.

If you are willing to take part in this study, please bring the signed copy of the enclosed consent form with you when you attend your outpatient appointment. If you have any questions or concerns, you can discuss these with the doctor at your appointment, alternatively please do not hesitate to contact me (see overleaf for details)

What are the side effects of taking part?

None, what we aim is for appropriate referral methods from GP surgeries to the Hospital. If your symptoms don't match the electronic protocol, your GP can still refer you using the existing methods.

What are the possible benefits of taking part?

You should not expect any direct benefit to your health or monetary wise. However the information we get from this study may help us to implement a valid referral method in future and streamline referral to hospitals.

Will my taking part in this study be kept confidential?

All the information that is collected about you during the course of the research will be kept strictly confidential. Any information about you, will have your name and address removed so that you cannot be recognised from it.

Your GP would however be aware of your participation in the study. The project has received ethical approval by the Dorset Research and Ethics Committee.

What will happen to the results of the research?

We would hope to be able to publish the results of this study in two years time. You would not be identified in any report or publication.

Contact for further information:

If you have any queries please contact:

Mr.Solomon John (Research Doctor) Telephone: 01202 303626 and bleep 2439.

e-mail: Solomon.john@rbch.nhs.uk

Fax: 01202 704613

Thank you for taking time to read this information sheet, which you can keep.

Please bring the signed consent copy for our reference.

Evaluation of Lower GI e-referral Protocol study

Consent Form: For Patient

	Patient No:
Name:	**Visit Date:**
Date of Birth:	**Hospital No:**

	Yes	No
Have you read and understood this information sheet?	☐	
Have you had the opportunity to ask questions and received satisfactory answers to all your questions?	☐	☐
Have you received enough information about this study?	☐	☐
Have you had sufficient time to decide whether to take part? in this study?	☐	☐
Do you understand that you are free to withdraw from the study At any time without giving a reason and without it affecting your future medical care?	☐	☐
Do you understand that your hospital medical records may be inspected by the research team, but your confidentiality will be protected.	☐	☐
I agree to my GP being informed of my participation in this study	☐	☐

Name of patient …….. Date: ……. Signature:……

Investigators name Mr Solomon John Signature: 

Department of Colorectal Surgery

"Lower GI e-Referral Protocol Study"

Dear Dr.Hearn,

Hope you are doing fine. This letter is just to remind you that patients with 'Lower Gastrointestinal Symptoms' and suspected 'Iron Deficiency Anaemia' could be referred using the decision support software on choose and book.

You could go with the decision support or override it if need be. The initial results with this pilot study look favourable. Please do get in touch with me if you require any information.

Hope to see some referrals from you through the "Lower GI e-Referral Protocol".

Thanking you,

Yours truly,

Solomon

Mr.Solomon John,
Research Registrar,
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