E-HEALTH: WEB-GUIDED THERAPY AND DISEASE SELF-MANAGEMENT IN ULCERATIVE COLITIS

IMPACT ON DISEASE OUTCOME, QUALITY OF LIFE AND COMPLIANCE

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PREFACE

The present Ph.D. thesis is based on 5 original papers:

I. Elkjaer M, Moser G, Reinisch W, Durovicova D, Lukas M, Vucelic B, Wewer V, Colombel JF,Shuhaibar M, O´Morain C, Politi P, Odes S, Bernklev T, Øresland T, Nikulina I, Belousova E, Van der Eijk I, Munkholm P. IBD patients´ need in health quality of care ECCO consensus. Journal of Crohn's and Colitis 2008; 2(2):181-8

II. Elkjaer M, Burisch J, Avnstrøm S, Lynge E, Munkholm P Development of a Web-based concept for patients with ulcerative colitis and 5-aminosalicylic acid treatment. Eur J Gastroenterol Hepatol 2010; 22(6):695-704

III. Elkjaer M, Burisch J, Voxen H V, Deibjerg K B, Jens-Kristian Slott Jensen S JK, Munkholm P. A new rapid home test for faecal calprotectin in ulcerative colitis. Aliment Pharmacol Ther 2010; 31(2):323-30

IV. Munkholm P, Michetti P, Probert CS, Elkjaer M, Marteau P Best practice in the management of mild-to-moderately active ulcerative colitis and achieving maintenance of remission using mesalazine. Eur J Gastroenterol Hepatol 2010 Aug; 22(8):912-6

V. Elkjaer M, Shuhaibar M, Burisch J, Bailey Y, Scherfig H, Laugesen B, Avnstrøm S, Langholz E, O´Morain C, Lynge E, Munkholm P E-health empowers patients with Ulcerative Colitis – a randomised controlled trial of the web-guided Constant-care approach Gut. 2010 Dec; 59(12):1652-61

BACKGROUND

Ulcerative Colitis (UC) together with Crohn's disease (CD) belongs to inflammatory bowel diseases (IBD). Incidence of IBD has been increasing during the last a few decades (1-3) resulting in more than 3 million people suffering from these conditions worldwide. Up to date IBD is as frequent as Insulin Dependent Diabetes (IDDM) and actually is second to rheumatoid arthritis (RA) in its chronicity (4).

Spite of intensive research, the aetiology of IBD is still uncertain. However, results from both genetic and environmental studies have pointed towards multi – factorial direction. One of the generally accepted hypothesis is a loss of immunological tolerance towards the bacterial intestinal flora of a genetically susceptible individual (5-7).

The natural history of IBD is highly diverse (25-27) and characterised by periods of unpredictable relapses interspersed with remissions (8;9).Treatment modalities including 5-ASA, corticosteroids, and immunomodulators as well as surgery have changed the natural history of the disease with respect to mortality and cancer occurrence in the bowel. However, first after introduction of the biological treatment at the end of 1990th improvement of the disease course by inducing mucosal healing has been observed (10). This new finding was a reason for proposal of a "top-down" model with Infliximab (11). However, this treatment is mostly used in severe cases, and it is still costly for the Danish Health Care (approximately 20.000 Euro/year/patient).

Langholz et al showed in the inception cohort from Copenhagen after 8 years from diagnosis of ulcerative colitis (UC) that 21%

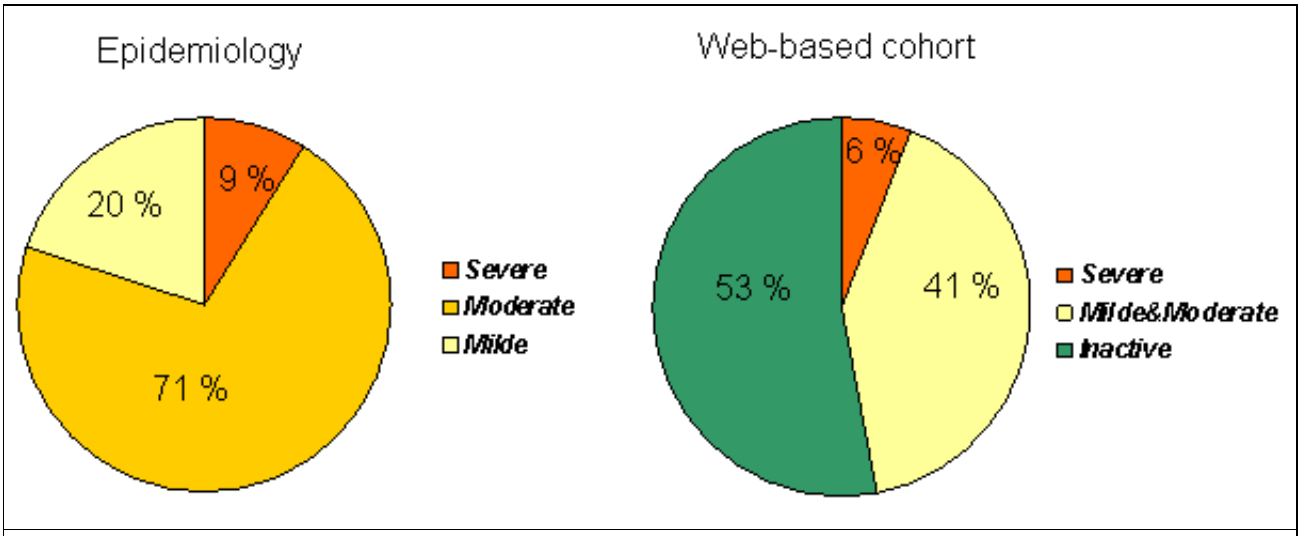

Figure 1
A) Disease activity in UC patients 8 years from the diagnosis in an inception cohort from Copenhagen 1962 – 1987 (12)
B) Disease activity based on the disease activity scoring (SCCAI9 in Danish UC patients (n=186) 1 year after initiating of the randomised web-based trial "Constant-care"

of patients have a mild and 70 % have a moderate disease course (12). This means that majority of UC patients are eligible for oral and topical (suppositories and enemas) 5-ASA treatment (fig. 1a + b). Moreover 5-ASA is well known for its low side-effect profile (13-15) and chemo preventive effect for colonic cancer (16).

In randomised control trials (RCT) with combination of high doses of systemic and topical 5-ASA treatment, the observed remission rates were up to 80-90% (15;15). But what is the current situation in the clinical setting? Unfortunately, the benefits of therapies reported in clinical trials (efficacy) are often reduced in a community-based clinical practice (effectiveness). Adherence (the extent to which the patient's behaviour matches agreed recommendations from the prescriber) is one of the factors affecting community effectiveness (17). The term adherence is commonly used together with compliance (number of pills taken as prescribed) and persistence (length of time taking the prescribed medication). However, each of them has a distinct meaning (18;19) (fig. 2).

Non-adherence in UC is a well known phenomena and is about 40-60% or even higher (20;21). In a recent publication, factors such as psychological distress, patients' beliefs in medications and doctor-patient discordance are associated with non-adherence in UC patients (22). Moreover it has been reported, that non-adherence is not only associated with 5-folds increased risk of relapse in patients with quiescent UC (23), but also with increased healthcare cost (24).

Non-adherence together with increasing number of patients requiring long-term care for other chronic conditions as well as for IBD could result in financial and staffing problems that Europe's healthcare may soon be facing. Therefore to maintain the same level of the quality of care, the EU-wide healthcare needs to be changed (25;26). Health authorities believe that development of the telebased services, which involves secure transmission of medical data and information needed for prevention, diagnosis, treatment and follow-up of patients can be the solution (27-29).

Telemedicine in form of web-based therapy has been developed for chronic diseases such as asthma (30;31), depression (32;33), diabetes (34-38), heart diseases and anticoagulation disorders (39-42) and alcohol addiction(43) . This new approach improved disease course, optimised patients´ adherence, compliance, quality of life (QoL), and reduced health care costs (44). However, there are still limited numbers of high quality studies in this area and such studies are completely lacking in IBD (Tab 1).

AIMS

The aims of this thesis were:

1) In a European evidence based consensus to state IBD patients' need in Quality of Health Care (QoHC) (Paper I)
2) To validate the influence of the Patient Educational Center (PEC) and web-based treatment solution program, www.constant-care.dk, on patients´ disease self-management, adherence and Quality of Life and compare the Web-UC patients' outcome of disease course after 1 year of self-initiated 5-ASA treatment with UC patients in a conventional out-patient setting (Paper II, IV and V)
3) To validate the usefulness of two new quantitative rapid tests: HT photo and RT scanning for development of a practical home test, for FC measurement, available for patients use (Paper III)

MATERIALS AND METHODS

IBD patients´ need consensus

The consensus was conducted on the initiative of the European Crohn's Colitis Organization (ECCO) and was defined as an agreement of 80% of participants (The Delphi method).The working group consisted of 11 doctors including one paediatric gastroenterologist and one psychologist; one sociologist, 4 IBD nurses, and 4 participants from the IBD patient organisations, including the chairman of the European Federation of Crohn's Colitis Association (EFCCA) from12 European countries and Israel. Most of the participants were members of ECCO and were invited to participate by chairman of the consensus Pia Munkholm, who is the head of EPICOM, the epidemiology group in ECCO.

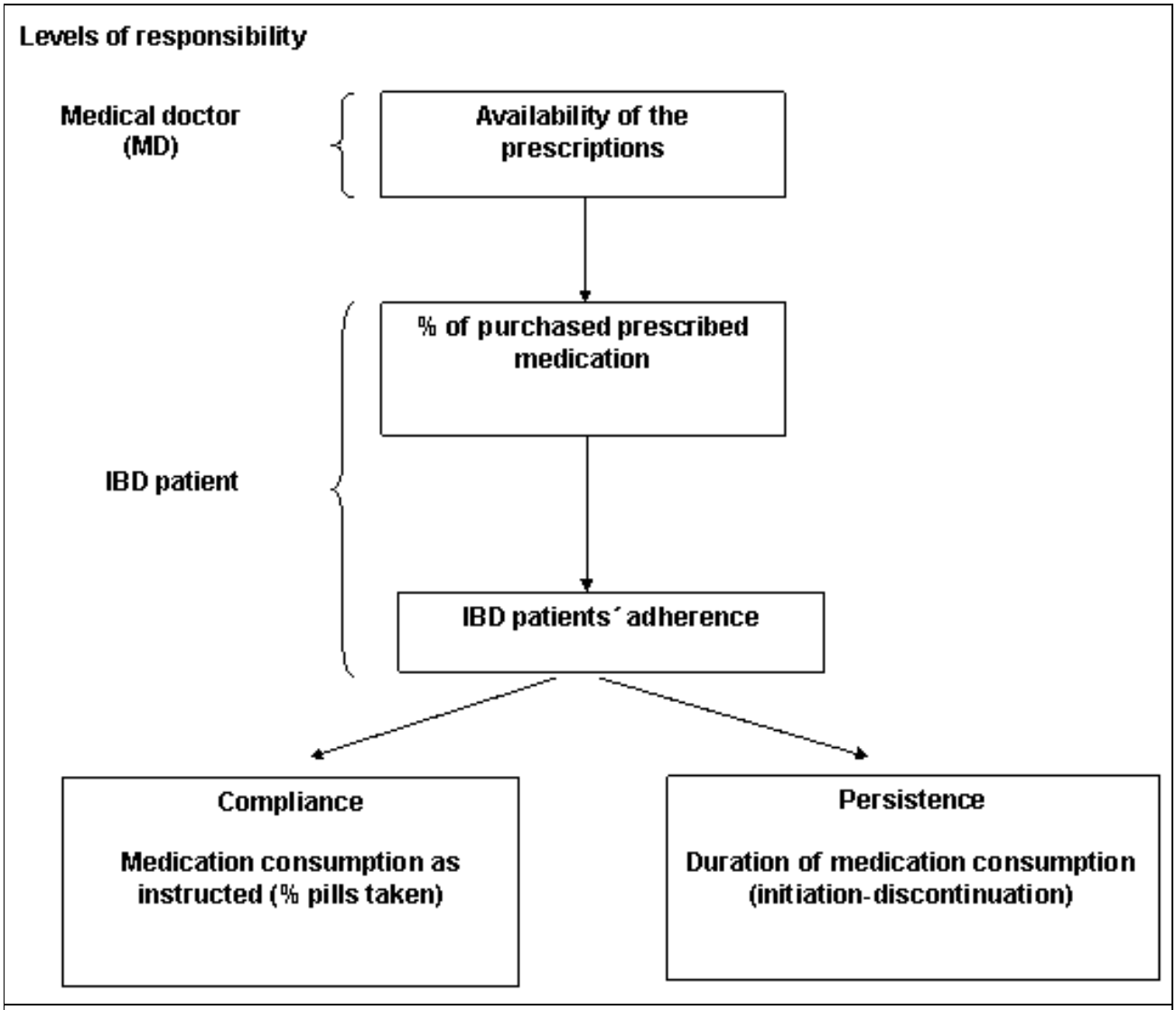

Figure 2
Levels of responsibility and flow of the prescription influencing adherence, compliance and persistence

The invita tions were based on their clinical and research expertise in the IBD care.

Disease related patient items: “Information”; “Education”; “Primary Care”, “Quality of life”, “Psychological help” and “Benchmarking of Health Care systems” were chosen by participants as background evidence for the consensus and involved systematic literature search in relevant databases.

Based on literature evidence preliminary statements were written by the first author. These statements were projected and revised on a screen during the next meeting, until a consensus was reached. Each recommendation was graded (RG) based on the level of evidence (LE) in accordance with the Oxford Centre for Evidence Based Medicine (45)(table 2).

The final consensus paper was written by the first author, edited for consistency before it was circulated and approved by the group.

Authors (year of publication) country	*Method*	*Number of patients*	*Disease/area*
Meyer et al (2009)[32] Germany	RCT	396	Depression
Van, Straten et al (2008)[33] The Netherlands	RCT	216	Depression, Anxiety and Stress
Van der Meer et al (2009)[31] The Netherlands	RCT	200	Asthma
Rasmussen et al (2005) [30] Denmark	RCT	300	Asthma
Postel et al (2010) [43] The Netherlands	RCT	158	Alcoholism
Van, Bastelaar et al (2011) [35] The Netherlands	RCT	255	Diabetes
Bond et al (2010) [36] USA	RCT	62	Diabetes
Cho et al (2006)[37] Korea	RCT	80	Diabetes
McMahon et al (2005) [38] USA	RCT	104	Diabetes
McManus et al (2010) [41] UK	RCT	527	Hypertension
Kashem et al (2006) [42] USA	RCT	36	Heart failure
Elkjaer et al (2010) (paper **V**) Denmark	RCT	333	Ulcerative colitis

Table 1
Overview of the randomised control trials (RCT), involving a web-based self-initiated treatment

Level	Individual study	Technique
1a	Systematic review (SR) with homogeneity of Level 1 diagnostic studies	SR with homogeneity of randomised controlled trials (RCTs)
1b	Validating cohort study with good reference	Individual RCT (with narrow Confidence standards Interval)
1c	Specificity is so high that a positive result rules in the diagnosis or sensitivity is so high that a negative result rules out the diagnosis	All or none
2a	SR with homogeneity of Level >2 diagnostic	SR (with homogeneity) of cohort studies
2b	Exploratory cohort study with good reference	Individual cohort study (including low quality standards RCT; e.g., <80% follow-up)
2c		"Outcomes" Research; Ecological studies
3a	SR with homogeneity of 3b and better studies	SR with homogeneity of case-control studies
3b	Non-consecutive study; or without consistently applied reference standards	Individual Case-Control Study
4	Case-control study, poor or non-independent reference standard	Case-series (poor quality cohort and case-control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"
	Grades of recommendation	
A	consistent level 1 studies	
B	consistent level 2 or 3 studies *or* extrapolations from level 1 studies	
C	level 4 studies *or* extrapolations from level 2 or 3 studies	
D	level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level	

Table 2
Levels of evidence and grades of recommendation based on the Oxford Centre for Evidence Based Medicine (May 2001), (45)

Development of www.constant-care.dk
Creation of a feasible, 24 hour a day available web-based treatment program for UC patients started in 2001 and was provided for this Ph.D. by the inventor PM (© www.constant-care.dk). The program was developed in Danish and English version and designed for patients with mild and/or moderate UC in 5-ASA treatment (systemic and topical) and topical prednisolon /hydrocortisone treatment only.

The program included the following site-index (figure 3):
"Welcome page" includes short introduction

"Intense symptoms" describes alarm symptoms, which should provoke urgent contact with the web-doctor. The symptoms are: More than 6 stools/day, daily rectal bleeding
(with every bowel movement), rectal bleeding occurring between relapses, fever > 37.5°C, heart rate > 90 per min, severe abdominal pain and/or tenderness, symptoms persisting for more than 11 days despite intensified treatment, and unexplained weight loss

" Evaluation" includes information about disease activity and effect of medication,

"Safety" describes the security level of admitted data and conditions regarding the handling of these data. Each user needs a unique username and password for accessing the program. Entering a wrong username or password for 7 times in a row will block access to the program. Only the web-doctor has access to patients´ data allowing continuous monitoring of patients disease activity treatment status, as well as the possibility to contact the patients, if necessary, to avoid complications

"Fill in forms" includes the following instructions: In case of a relapse, patients are requested to log on daily and fill in the Simple Clinical Colitis Activity Index (SCCAI) until they enter the green zone (remission). Hereafter the patients are requested to log on once a week for a total of 4 weeks after the start of the relapse. The short Inflammatory Bowel Disease Questionnaire (s-IBDQ) should be filled in at the beginning and at the end of each relapse. Once remission is achieved the patients have to use the program (fill in SCCAI and s-IBDQ) once a month until the next relapse occurred. Moreover, a guidance regarding collection and posting of faecal samples for FC measurement, in case of relapse and remission included.

"Data input" shows the registration status

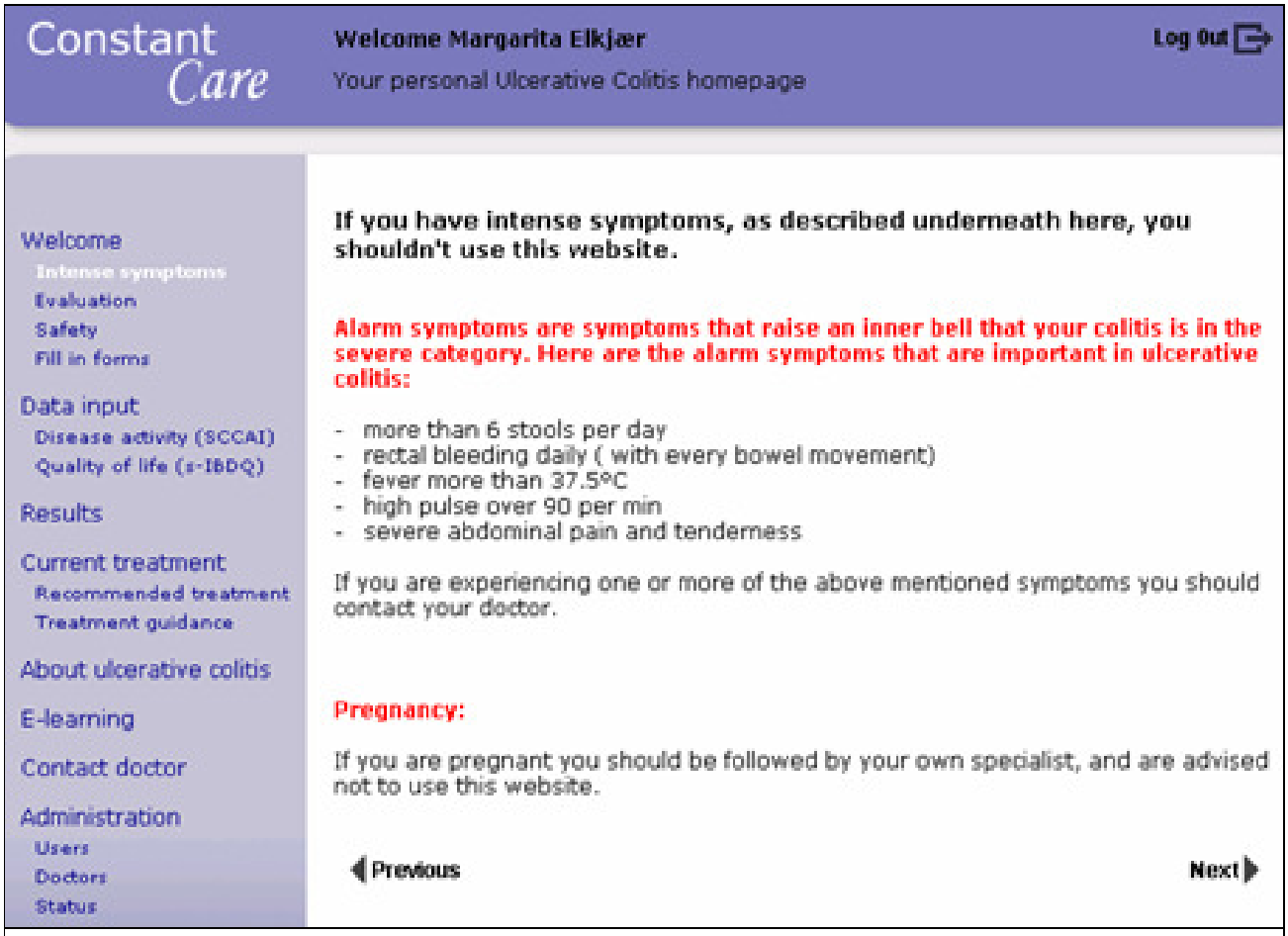

Figure 3
The site-index of the web-program from "Constant-Care" (paper II)

"Disease activity (SCCAI)" consists of 6 items to be completed

"Quality of life (s-IBDQ)" consists of 4 disease specific items to be completed

"Results" includes illness status in a graphical form. All stored information regarding the disease activity and QoL during the last four weeks appears on the web program. Earlier saved information can be retrieved by the patient and the doctor, allowing for disease history follow up

"Current treatment" includes patient's treatment at present time

"Recommended treatment" includes web-programs treatment recommendations depending on the illness status calculated in "Results" as well as patient's "Current treatment"

"Treatment guidance" includes information regarding acute and maintenance treatment of UC

"About ulcerative colitis" consists of general information about ulcerative colitis for the patients

"E-learning" consists of 8 specific questions regarding 5-ASA treatment, each with 3 possible answers. Correct answers appear in "green" and wrong answers appear in "red" colour with a cumulative percentage of the wrong answers. The program can be reset, which allows the patient to test his/her knowledge several times, until 100% correct answers are obtained

"Contact doctor" includes web-doctor's contact information (e-mail address and cell phone number), so the web patients can contact the web-doctor by sending an e-mail directly from the web-page or call/send a text message

"Administrator page" is only available for the web-doctors use for the "web-ward rounds"

The key element of the web program is an automatic cumulating data system, consisted of the disease activity scoring from SCCAI (46) and quality of life from s-IBDQ (47) chosen by patients on the site-index. When the patient completed the SCCAI, patient's disease activity status will appear in a graph as a simple traffic light, where "red" indicates highly active UC, "yellow" moderate active UC, and "green" quiescent disease. Completed s-IBDQ will also be shown as a graph, where "red" indicates poor and "green" god quality of life (figure 4 and 5).

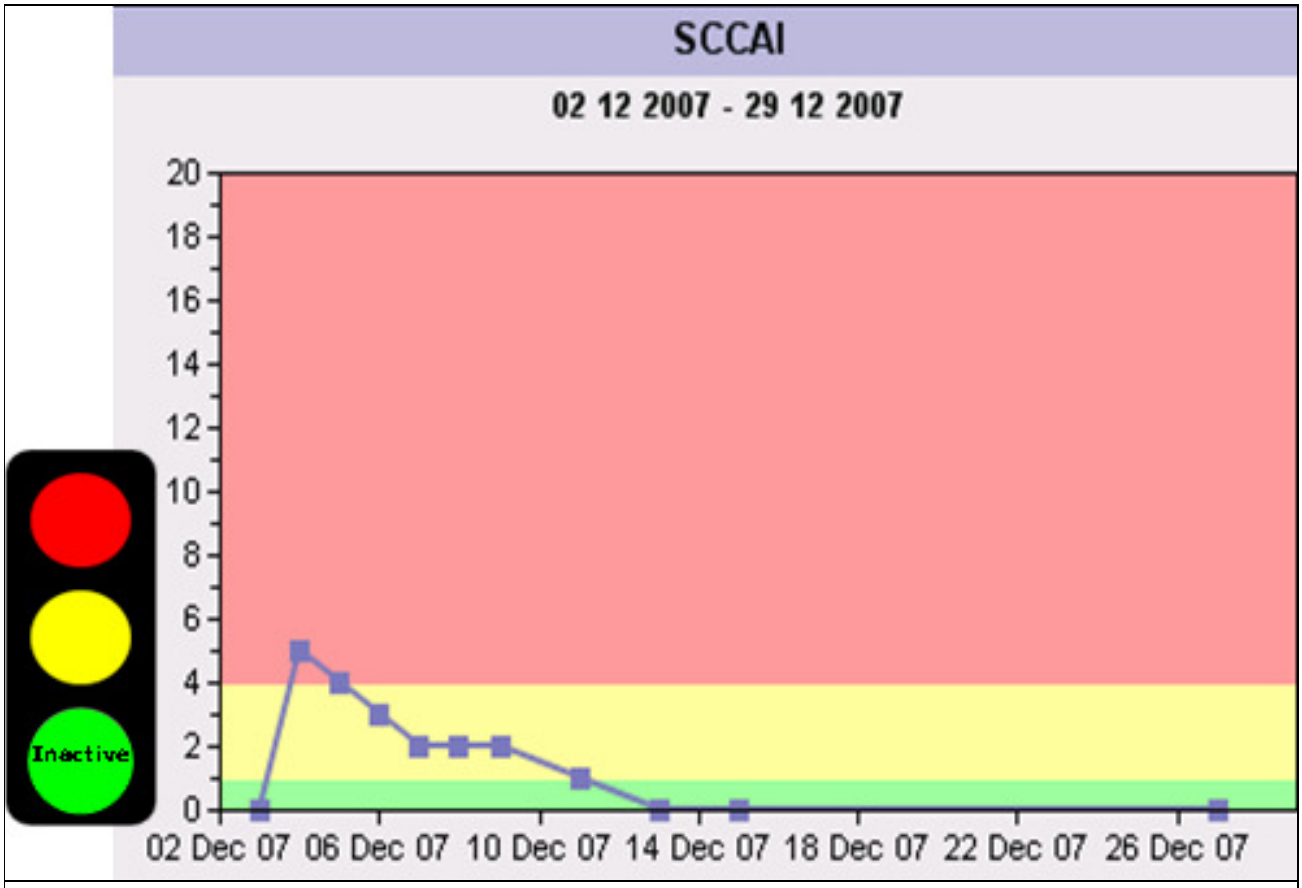

Figure 4
Example of disease activity course during 30 days from the occurrence of relapse. Simple Clinical Colitis Activity Index (SCCAI) is completed by the patient in the web program "Constant care" and results are automatically cumulated after each insertion (paper II)

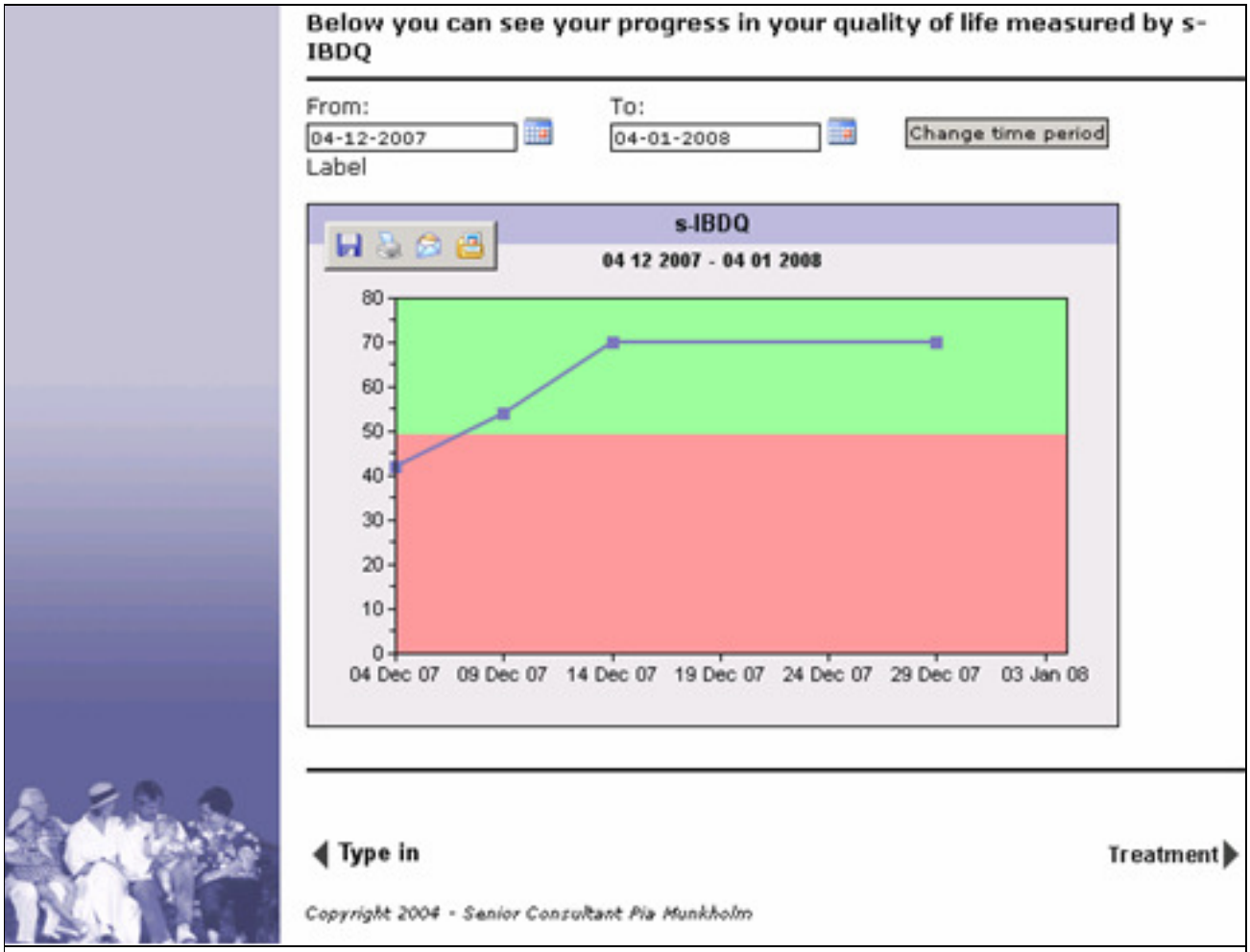

Figure 5
Disease specific Quality of Life Questionnaire (s-IBDQ) is completed by the patient in the web program "Constant care", and results are automatically cumulated after each insertion. "Red" indicates a poor and "green" a good quality of life

Patient Educational Center (PEC)

Prior to the study we developed Patient Educational Center (PEC) in our department (Gastrointestinal Unit, Medical Section, Herlev University Hospital). The staff of the PEC consisted of 4 IBD nurses, 1 consultant (PM), and Ph.D. student, MD (ME). To educate the patients in a proper way a user friendly board with original 5 - ASA products and topical steroid medication from all available companies in Denmark was constructed (Figure 6).

Furthermore, we prepared binders for the patients, which included slideshows, information of pharmacies opening hours, daytime "IBD helpline", doctor contact information, a "Constant-care" calendar, information about 5-ASA treatment and side effects, and a booklet from the Danish Colitis Crohn Organisation.

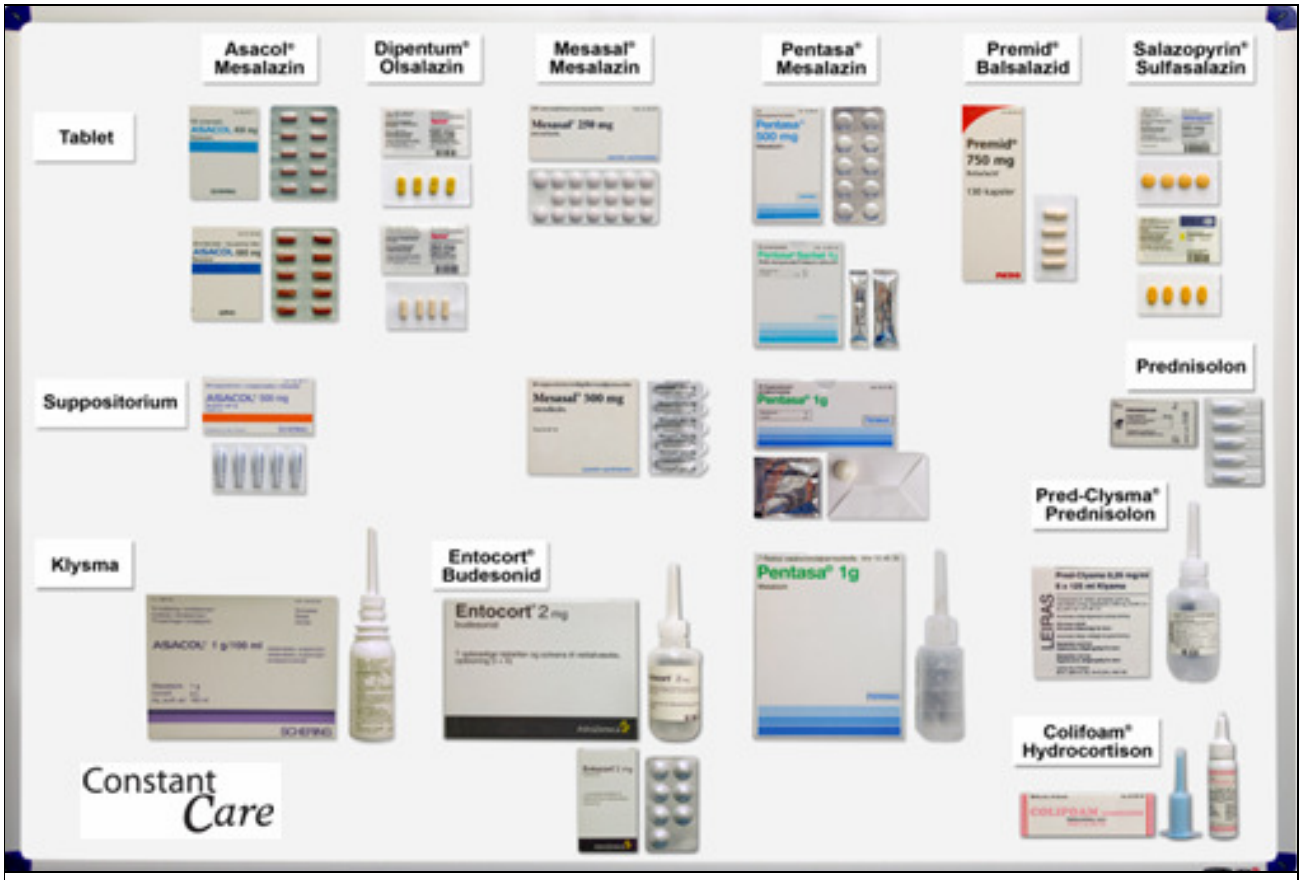

Figure 6
A user friendly educational board with original packing of 5-ASA and topical steroid medication (paper II)

Faecal Calprotectin (FC)

FC is a calcium-binding protein which constitutes 60% of total protein in the cytosol fraction of human neutrophils and furthermore has antimicrobial and antiproliferative effects (48-50). It was first described by Fagerhol et al in 1980 (51). Later in 1992 the original Enzyme-linked immunosorbent assay (ELISA) for FC measurement was in the first time described by Røseth et al (48). Since the ELISA method has been thoroughly validated and is currently used as the "Gold Standard" for detection of intestinal inflammation in faeces (52).

The intention of the trial described in paper III was to develop a practical home test for FC measurement, available for patients use in the future e-Health systems. In paper V FC was determined by ELISA and applied to evaluate eventually over-treatment of the patients by the web-care system. However, both patients and investigators were blinded for the results until end of the study. FC measurement by ELISA was according to the manufacturer's instructions (Calprest®, Eurospital SpA, Trieste, Italy, provided by Calpro AS, Norway). In brief: all received stool samples were registered and stored at -20 ºC. After thawing, between 40 -120 mg of stool were collected and placed into a sample tube containing a spiral coil (Roche Diagnostics GmbH, Germany). Then we added a pre-diluted extraction buffer in a weight/volume ratio of 1:50. The sample tubes were mixed for 30 seconds and then homogenized for 25 minutes. After transferring of one ml of the homogenate to an Eppendorf tube, it was centrifuged for 20 minutes at 10.000 G. The final, supernatant of 0.5 ml was transferred to a new tube and stored at -20 ºC for up to three months prior to analysis.

In paper III the following method, for the new quantitative rapid tests, was used:

The thawed supernatant was further diluted with dilution buffer in a ratio of 1:10 and 115µl of this extract was applied onto the application window of the Lateral Flow Device (LFD), where a special combination of monoclonal anti-calprotectin antibodies and affinity purified rabbit polyclonal antibodies is used. Moreover, this test device contains a nitrocellulose membrane where antibodies against calprotectin are covalently bound in the Test-line (T) position and to a control antibody in the Control-line (C) position (Photo 1).

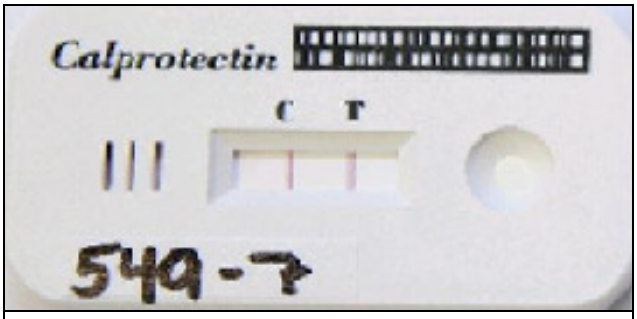

Photo 1
Lateral flow device (LFD) for faecal calprotectin measurement with the test (T) and control (C) lines and the bar codes, used in the rapid test (paper **III**)

When the sample is placed onto the conjugate pad, "a small window" on the right side of the LFD the gold-labelled anti-calprotectin antibodies bind to the calprotectin in the sample and diffuse across the membrane. After 10 minutes of incubation the colour intensities of the T- and C - lines were scanned, read and calculated by special software Calproscan from Calpro AS, Norway (Photo 2) and then showed on the lap-top screen (Photo 3).

Photo 2
The rapid test (Scanning model) (paper **III**)

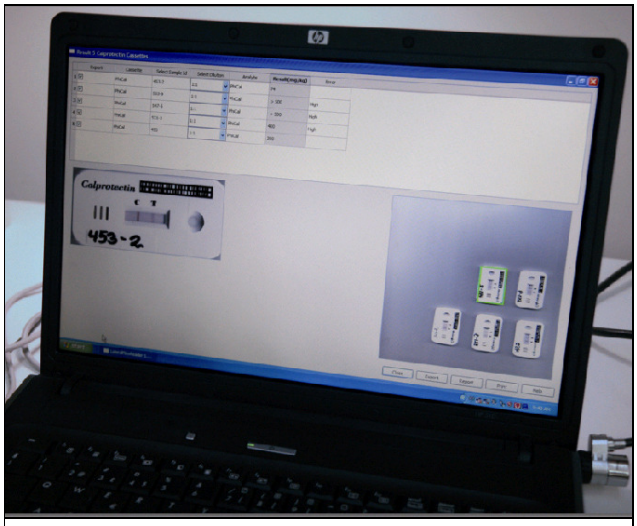

Photo 3
Faecal calprotectin results (mg/kg) showed on a lap-top computer screen (paper **III**)

For the home test (HT photo) we took a picture of the same LFD, just after the scanning procedure, using a mobile phone with a 3.2 m pixel auto focus camera. Then this picture was sent to a server in Oslo (Calpro AS, Oslo, Norway) via Mobile Internet, by means of a special software package. The result, in mg/kg, appeared on the phone display after 15 seconds (Photo 4).

Photo 4
The faecal calprotectin result (mg/kg) appears on the phone display 15 seconds after the picture has been taken (paper III)

RANDOMISED NON-BLINDED CONTROLLED TRIAL (RCT) "CONSTANT-CARE"

Patients' selection

After approval from the ethical committee, patients aged 18 to 69 fulfilling the international diagnostic criteria for mild/moderate UC, treated with 5-ASA, were selected from the Danish Crohn Colitis Database at Herlev and Amager Hospital, Copenhagen, Denmark and patient records at Adelaide and Meath Hospital in Dublin, Ireland. Patients were contacted by letter and invited to participate in the study. The patients were included prospectively between March 1 2007 and December 15 2008 in Denmark and between May 1 2008 and January 22 2009 in Ireland. Information regarding demographic data, treatment, tests results, absence due to UC and visits in the out-patient clinic was recorded in the patients' case record form (CRF). At the end of the study all patients' hospital records were scrutinized. All patients were followed for 12 months.

Diagnostic criteria

Copenhagen diagnostic criteria for UC proposed by Langholz et al (53) (all three of the criteria must be present):

1. History of diarrhea and/or rectal bleeding and pus for more than one week or repeated episodes.
2. Characteristic endoscopic findings of continuous ulceration, vulnerability, or granulated mucosa.
3. Histopathology consistent with UC (neutrophils within epithelial structures, cryptitis, crypt distortion, crypt abscesses).

Intestinal infection and cancer must have been ruled out.

Exclusion criteria were:

- acute phase of co-morbid conditions (such as rheumatoid arthritis, chronic lung disease, coronary heart disease, chronic pancreatitis)
- drug (narcotic) dependence or substance abuse
- use of immunomodulator (such as azathioprine, 6-mercaptopurine, metrothrexate or anti-TNF therapy)
- frequent treatment (>6 months/year or 2 treatments per year) with high dose of corticosteroids to enter remission
- likely requirement of IBD surgery during the study period or previous IBD surgery
- pregnancy or breastfeeding
- inability to read or understand the informed consent or to use a computer

Eligible patients were randomly allocated either to the interventional (web) group or to the control group by use of a randomisation program. Before patients´ inclusion each randomisation number was put into a closed, consecutively numbered envelope by two nurses, not participating in the study.

At the end of the study we included a historical control group (HCG) to test the comparability with the randomised control group. In Denmark inclusion of the HCG was carried out retrospectively from Gentofte Hospital. In Ireland the HCG was included prospectively from Adelaide and Meath Hospital.

PROCEDURES

Web-intervention

The web-patients were educated in the Patient Education Center (PEC) by investigators: ME in Denmark and MS in Ireland. Educational training (ET) included 3 hours of education, where the first 1.5 hours were used on a disease specific presentation and the second 1.5 hours were used on theoretical and practical training in using www.constant-care.dk with one person per computer.

The primary goal for the investigators during the education was to ensure that each web-patient understood the concept, was able to recognise a relapse and to start the correct treatment, guided by the program. We did not change the planned routine visits in the out-patient clinic. However we informed the web-patients about a possibility to cancel their appointments, if they felt secure during the web-based treatment. The web-patients were asked to log on to www.constant-care.dk and follow the web-program recommendation at the same day after ET.

Medical treatment on www.constant-care.dk

In table 3 all medication and dosages available for the treatment on the web-program during the study is presented.

In case of symptoms as “rectal bleeding” and/or “more than 3 bowel movements/day” and/or ”nightly stools” the program recommended acute systemic treatment with 4 gram daily of 5-ASA or more for a maximum of 28 days, with the option to extend the high dose period with further 28 days after investigators´ evaluation, if remission (green zone) had not been achieved (15). Moreover, the patients have been informed that use of the local treatment was compulsory during the relapse and should be used together with the systemic treatment. When patients achieved remission again, the system recommended changing the acute treatment to a maintenance therapy.

Control patients

Patients in the control group continued the conventional treatment and follow up in the IBD out-patient clinic. However, during the baseline visit, all control patients were instructed to fill in the SCCAI and the s-IBDQ in a paper form, and send them to the investigator in case of any symptom indicating a relapse, as rectal bleeding or/and more than 3 bowel movements per day or/and nightly stools. These questionnaires were marked with red colour. The patients were also instructed to fill in the same questionnaires (marked with green colour) at absence of symptoms, and send the questionnaires 7 days latter, to be sure that they had obtained a stable remission.

All questionnaires included labels for the dates. Thus, it helped us to control length and frequency of relapses in the control group.

Outcomes measures

After the inclusion, randomised patients had 3 visits: at baseline, at 6 months, and at 12 months. At each visit, they were asked to fill in 7 questionnaires, where 2 of them were constructed at the Herlev University Hospital; the Compliance Questionnaire (CQ) and the Satisfaction VAS Questionnaire (SQ). The other 5 questionnaires were all internationally validated; the Crohn Colitis Knowledge Score (CCKNOW), the s-IBDQ, the SCCAI, the Health Survey (SF- 36/SF-12), the Hospital Anxiety, and the Depression Scale (HADS).
All questionnaires are presented in Appendix I.

Faecal Calprotectin (FC): All patients were asked to send a stool sample for FC measurement at each visit, relapse and again 7 days after absence of the relapse symptoms. FC results connected to relapse were blinded for both investigators and patients until end of the trial. To identify possible over treatment we compared the SCCAI with the FC results.

Stool samples: All patients were asked to collect a stool sample and send it to the study investigator at the entry examination and at each relapse for analysis for pathogenic bacteria, Clostridium Difficile (Cl. dif.), ova, worms and cysts.

Blood test included: haemoglobin, liver, pancreas and kidney function and inflammation markers. These blood samples have been screened at least annually.

Endoscopy: Patients from the intervention groups did undergo sigmoideoscopy/colonoscopy if patients did not respond to acute treatment. In the control group the need of endoscopy was evaluated by the attending physician.

MEDICATION	RELAPSE			REMISSION		
	Tablets/Caps (mg/day)	Suppositories (mg/day)	Enemas (mg/day)	Tablets/Caps (mg/day)	Suppositories (mg/day)	Enemas (mg/day)
Asacol	4800	500	1000	2400	500	1000
Colifoam hydrocortisone (foam)			100			
Dipentum	2000			1000		
Entocort			2			
Mezavant	4800			2400		
Mesasal	4000	500		1500	500	
Premid	6750			3000		
Pentasa	4000	1000	1000	2000	1000	1000
Prednisolone		10	31.3			
Salazopyrin	3000			2000		

Table 3
Medication and dosage recommended by www.constant-care.dk (paper **II**)

STATISTICAL ANALYSES

All statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago IL) and SAS version 9.1 and 9.2 (SAS Institute, Cary, NC, USA). A p-value of <0.05 was considered statistically significant.

In paper II

Before and after the educational training:

- The paired student T-test was performed to compare results from s-IBDQ, SF-36 and HADS
- The difference between proportions of right answers of all cases from CCKNOW was analyzed by "Z" based statistical test.

Simple descriptive analyses regarding VAS and Validation Questionnaire were performed.

In paper III

The binomial proportions sensitivity, specificity, positive and negative predictive values (PPV, NPV) were calculated by using the following formulas: NPV [TN/ (TN+FN)], PPV [TP/ (TP+FP)], SENSITIVITY [TP/ (TP+TN)], SPECIFICITY [TN/ (FP+TN)], where T = True, F = False, N = Negative, P = Positive. Exact 95% confidence intervals were calculated for the binomial probabilities. The quantitative ELISA test was used as reference ("the gold standard").

Calculation of the mean differences between the assays were based on 'Statistical methods for assessing agreement between two methods of clinical measurement' (54). 95% confidence intervals and limits of agreement were calculated using normal distribution theory (55). We chose a cut-off level of the mean difference of ±500 mg/kg with a range of 3000-1000 mg/kg.

Intra- and inter-patient assay variability was assessed by kappa (k) variance analyses estimating the agreement in excess of the agreement that would be expected by chance. For the overall assessments, variance homogeneity among assay was assumed.

In paper V

We analysed the data as intention to treat, which is a strategy for the analyses of RCT that compares all patients in the groups to which they were originally randomly assigned, regardless of whether they actually satisfied the entry criteria, received the treatment, or subsequently were withdrawn from the protocol. Time from the first relapse to remission and start of acute treatment at relapse were analysed by log-rank test and displayed by Kaplan Meier curves. For calculation of the compliance data Chi-square test was used. We used Fisher's exact test and Student's T-test for comparison of the two trial arms with respect to frequency and duration of disease progressions. McNemar's test (a

non-parametric method used on nominal data and is applied to 2 × 2 contingency tables with a dichotomous trait and matched pairs of subjects, to determine whether the row and column marginal frequencies are equal "marginal homogeneity"), was used to compare disease activity and calprotectin measurements between the groups. Fisher's Exact Test was performed to compare results from CCKNOW, s-IBDQ, SF-36 and HADS. Moreover, Fisher's exact and Wilcoxon tests (a non-parametric statistical hypothesis test for the case of two related samples or repeated measurements on a single sample) were used for the comparison of patient's characteristics. We performed simple descriptive analyses regarding Validation Questionnaires.

RESULTS AND DISCUSSION

IBD patients need in Health Quality of Care, ECCO Consensus (paper I)

Result

In this paper we described, that the definition of Quality of Health Care varies throughout the World and correlating with the Gross National Product (GNP) and health care economics. A standardised definition of general Quality of Health Care in Europe has been developed and used (56) based on current medical evidence. Recently EC-IBD representing 12 countries throughout Europe clearly showed that Quality of Care directly influences Quality of Life of patients with IBD (57), (fig 7). However, during the conduction of this consensus and at "the round table" discussion it became evident that not only Eastern but also some Western European countries have difficulties in this field. These difficulties included long waiting times for consultation with IBD specialists, absence of IBD nurses, absence of "help-lines" and phone consultations, even in cases of long distances between the patient and the health care provider, and lack of access to best available treatment.

In this consensus the IBD patients' need of Quality of Health Care in Europe defined and outlined in seven ECCO statements (from A to G), which were conducted of 76 articles fulfilling the pre- defined search criteria described earlier in materials and methods.

ECCO Statement A

Quality of Health Care depends on level of disease information available to the patient with IBD. The provision of patient-centred information is strongly recommended [EL 1b, RG B]

ECCO Statement B

IBD-related education influences Quality of Health Care through increasing Health Related Quality of Life, compliance and adherence [EL 1b, RG A]

ECCO Statement C

Quality of Health Care in IBD is different in primary care in Europe and should be standardised [EL 2a, RG C]

ECCO Statement D

Health Related Quality of Life is related to Quality of Health Care, disease activity, psychological status, stressful life and social support [EL 2b, RG B]

ECCO Statement E

Physicians should assess (IBD) patient's psychosocial status and co-ordinate additional psychological care and recommend psychotherapy when indicated. Integrated psychosomatic care should be provided in IBD centres [EL 2b, RG B]

ECCO Statement F

Quality of Health Care implies patients' involvement, technical safety and Quality of medical standard to insure best practice in IBD. Benchmarking should be used to assess this [EL 2c, RG B]

ECCO Statement G

Children and adolescents need special attention to increase Quality of Life and Quality of Health Care: Access to multidisciplinary paediatric specialist teams including paediatric psychologist, dietician and social worker is mandatory. Age related information and education is important [EL 2b, RG C]

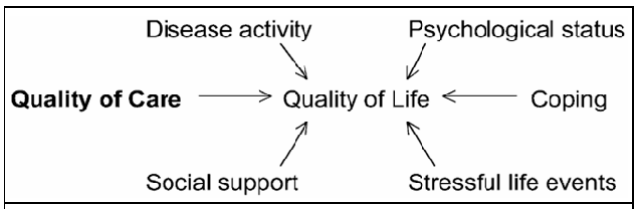

Figure 7
The influence and interaction between Quality of Care and Quality of Life and other events in the IBD patients´ life (57)

Discussion

The results presented in paper I clearly showed, that evidence-based medicine in Quality of Health Care (QoHC) is limited and generally low. However, it is evident that optimisation of QoHC by "information"; "education", "benchmarking" and "psychological analysis" helps to improve patients´ compliance, increases Quality of Life, and decreases depression and anxiety.

The ECCO board decided that this consensus should not include topics such as medical and surgical treatment, Complementary and Alternative (CAM) treatment, and nutrition, as these topics had been discussed in earlier published ECCO consensus documents on CD and UC: special situations (58;59).

Based on the evidence and experiences from different countries, the ECCO Quality of Health Care group proposed future aspects regarding optimisation of QoHC in IBD (Table 4). One of suggested entity was E-health that hypothetically could increase patients´ adherence, compliance, and persistence via self-initiated therapy.

However, we have to be aware that some of the proposals as for example Proper Health Economics could be difficult to fulfil in all countries and at all times. Nevertheless, we believe, that this consensus could be a helpful tool in providing a better care for IBD patients throughout Europe. The consensus is now available as free download from www.ECCO-ibd.eu and can be retrieved as an App´s on your iPhone.

NEED OF
Increase of general knowledge
1. In public and primary care through National TV and Radio to avoid "Patients delay-doctors delay"
2. Consensus of simple guidelines to GP´s (European Primary Care)
Proper access
1. To the IBD clinics & specialists
2. To "Help-line"
3. To adequate time at consultancy at the specialist & IBD nurse
4. To choose gastroenterologist at patients´ needs
Proper information & education for patients
1. Level of information has to fit patients´ different needs in different life cycles
2. Disease related written Information in IBD clinics, GP´s and pharmacy
3. PEC, patient education centre for patients and relatives
4. Patient organisation courses for patients and relatives
Proper education for medical providers
1. Recommend IBD nurse curriculum at European level (ECCO)
2. Recommend IBD nurse network
3. ECCO courses for any specialist
4. Minimal standard for IBD specialist – ECCO Homepage: www.chronic.disease.mangement
Proper Health Economics
1. Health Care authorities should facilitate the development of IBD network
2. Health insurance has recognized IBD patients as complicated patient group needing special care
3. Recommend maximum reimbursement of medical treatment and psychological care
4. Employment rates should be kept high by the public 5. Encourage studies to assess if Quality of Health Care is economical

Table 4
Future aspects in optimisation of Quality of Health Care in IBD (paper **I**)

Web-based treatment approach in UC (paper II, IV, V)

As previously mentioned the web-based therapy has been successfully developed for other chronic diseases, which improved disease course, optimised patients´ self-adherence, compliance and quality of life (QoL), as well as reduced health care costs. However, this type of therapy has never been described in IBD. At the present time in our clinic in the case of relapse patients do not have access to the out-patient clinic during holidays, weekends and during patients' vacations or business trips. Therefore a program available 24 hours a day, which can recognise a relapse and guide patients to optimal 5-ASA treatment, could be an important supporting factor for optimising therapeutic efficacy and community effectiveness.

Paper II aimed to describe the development of the concept "Constant-care" including the web-based treatment solution www.constant-care.dk and the Patient Educational Center. The purpose was furthermore to test the feasibility of using the program, the length of the education, and the use of the large number of questionnaires before the randomised control trial was initiated.

Paper IV aimed to summarise several elements of mesalazine management from the patient perspective based on a range of clinical and patient-focused evidence, primarily for the clinicians.

Paper V aimed to validate the influence of the Patient Educational Center (PEC) and the web-based treatment solution program, www.constant-care.dk on patients´ disease self-management, adherence and Quality of Life as well as to compare the outcome of the Web-UC patients' disease course after 1 year of self-initiated 5-ASA treatment with UC patients in a conventional out-patient setting in Denmark. In Ireland, we primarily aimed to validate the concept with English speaking patients.

Results (paper II)

The 1st validation (group A) prior to RCT

Twenty UC patients regardless of activity and type of the disease and of medication were asked to participate in the study. Half of these rejected participation due to lack of time. Ten consecutive UC patients with median disease activity score of 4.5 (range 0 -10) participated in the educational training (ET) session (table 5). All patients reported after the ET that they felt capable to initiate treatment. Ninety percent gave positive feed-back regarding the level and relevance of the ET. No patients experienced any difficulties regarding wording of the content of the E-Learning program. None of the participants reported any problems connected to the stool sampling, and 67 % found it relevant. Half of the patients concluded that the CCKNOW questions were too difficult 5.5 cm (range 4-10), but the length of the education was "acceptable". Comparison of the level of CCKNOW knowledge before vs. 3 hours after the education showed a significant increase in correct answers from 36 % to 69 %.

The 2nd validation (group B) 3 months after start of the RCT

Eleven web-randomised UC patients from the trial (median disease activity score 1 (range 0-3)) were asked to validate the concept, as a group, 3 months after the education in the RCT (Table 5).

VARIABLES	GROUP A	GROUP B
Total patients	10	11
Sex f/m	4/6	4/7
Caucasian	9	11
Age (yr): Median (range)	39.5 (25-67)	42 (25-60)
Duration of disease (yr): Median (range)	2 (1-7)	7 (0.5-33)
Disease extent at diagnosis (%) Proctitis Left sided Pancolitis	30% 30% 40%	9% 64% 27%

Table 5
UC patients' characteristics in the validation groups A and B (paper II)

All patients reported capability of self-initiated treatment after the ET. Seventy percent of patients did not experience any changes in QoL. However, 60 % and 100 % respectively reported an increase in quality of treatment and knowledge of the disease. All participating patients responded positively regarding the level and relevance of the ET, without any difficulties regarding the wording content of the E-Learning. In this group 70 % of patients had no problems with collecting of stool samples, and 90 % found it relevant. As in group A, 1/2 of the patients felt that the CCKNOW questions were too difficult; 5 cm (range 0-6), but the length of the education was "acceptable". The level of CCKNOW knowledge before vs. 3 hours after ET increased significantly from 28 % to 75 %. Depression and anxiety score, disease related and general QoL did not show any difference in both validated groups (A and B).

Discussion

In paper II validation of a new virtual concept for UC patients - "Constant-Care" including the web-program www.constant-care.dk and the patient education centre (PEC) is presented. To our knowledge the www.constant-care.dk is the first Web-based treatment solution program for UC patients, where the patients can follow the disease history and are allowed to be actively involved in the disease management. This concept was initially tested on 21 patients. All patients reported ability to self-initiated treatment after participating in the ET. Among the initially 10 educated patients, 8 expected that the concept would increase their QoL and quality of treatment. Among the later educated 11 patients, all of them experienced increased knowledge of the disease, 6 of them experienced increased quality of treatment, while only 3 reported an increased QoL.

Information and education of IBD patients have earlier been shown to increase compliance and QoL (60;61). In study done by Robinson et al (62) showed that after 15-30 minutes of personalised training of UC patients 96 % of documented relapses were self-treated. Moreover, the self-management of the disease significantly reduced number of out-patient visits. Our concept included 3 hours of disease and web-specific education for both patients and their relatives, as we strongly believe that involving patients´ relatives in the educational process will give a necessary support to the patients. Involvement of relatives resulted in positive feed-back from both patients and relatives. However, we did

not aim to test the relatives in any way. Most of the patients were satisfied with the level and duration of the educational training, which significantly increased patient's disease specific knowledge. However, we have to point out that the patients´ knowledge was validated after 3 hours, which is a rather too short time interval. There were two reasons for our choice: 1) the primary aim of this pilot study was to test feasibility of the "Constant-Care" concept; and 2) patient time and our time were limited before starting the RCT.

As we expected, patients` QoL, Anxiety, Depression and General well being, did not show any significant difference after educational training. The results of this pilot study have been taken into account for the planning of the RCT. We modified the slide kit and the patients´ educational binders. Furthermore, we implemented minor functional adjustments to the web-program. Our experience from the study resulted in reduction of the size of the educational groups, so computers were available for each patient during the education. As changes of the concept were minor, we decided do not validate them again in the RCT.

Results (paper IV)

This review aimed to go through the current literature of mesalazine treatment of patients with mild/moderate UC and was the basis of dosage, modality and length of treatment chosen for the web-based treatment solution. The results clearly showed that patients wish to be in remission and to have a promptly access to specialist care (57). Actually, patients are often prepared to accept higher risks from medical treatment to avoid undesirable outcomes such as colectomy (63). The indirect cost of UC seems to be high, since up to 70 % of patients reported that symptoms can affect leisure activities and job function (64). It is evident that appropriate treatments lead to improved QoL and an increased likelihood of returning to paid employment (65).

As earlier reported in patients with mild-to-moderately active proctitis, topical mesalazine 1g/day is recommended as first-line therapy (66), which is more effective than either rectal steroids or oral mesalazine alone (67;68). Patients with distal and extensive colitis achieved remission rates of 89% by using a combination of oral and topical treatments (15). The generally acceptable optimal dose for oral administration is between 2 and 4.8 g/day (66). However, it is still debatable, if there is a dose response in acute UC. The majority of patients can be maintained in remission using oral once-daily mesalazine therapy, which also can improve patient satisfaction and possibly compliance (69-71). Poor compliance is still a problem, especially in quiescent UC. Furthermore it can lead to a five-fold greater risk of disease flare-ups (23). One of the most frequent reasons for poor compliance is forgetting to take medication (stated by >90 % of patients) (72). Moreover we, as clinicians, need to consider a patient's payment ability in situations where patients do face prescription co-payments, and whether this will influence a patient's compliance (73). Also we have to consider the importance of costs in both maintenance therapy and active disease, as it has been shown that in adherent patients treatment costs were reduced by 13 % compared with non-adherent patients (74).

Discussion

In this review we summarised several elements of mesalazine management from the UC patient's perspective based on a range of clinical and patient-focused evidence. Our results have supported treatment statements of proctitis, left sided and extensive colitis as stated in the ECCO consensus (66). For the management of proctitis rectal mesalazine suppository 1g daily should be the first-line therapy. For proctitis and distal disease, the addition of oral mesalazine at 2–4 g daily may provide additional clinical and patient-relevant benefits. For extensive disease a combination of oral (2–4 g) and rectal mesalazine (1 g) per day should be the mainstay of treatment.

However, from our clinical practise we know that subgroup of relapsing UC patients response better to higher doses of 5-ASA (e.g. 4.8 g of Asacol). This trend of dose-response is also confirmed for active UC in meta-analysis by Sutherland et al (75). Furthermore, the ASCENT II trial in 268 patients with moderately active UC, showed significantly better treatment response in the 4.8 g Asacol group (71.8 %) compared to the 2.4 g group (59.2 %), p=0.036. As no increase in side-effects by using high doses was observed, the higher doses of 5-ASA are recommended by ECCO (66).

Once-daily (OD) mesalazine therapy is at least as effective as more frequent dosing in both the induction and maintenance of remission in UC. Oral mesalazine at 2 g is proofed to be effective in maintenance of remission. In a recent study by Kruis et al 3.0 g OD of mesalazine showed to be the most effective dose for maintenance of remission compared with lower or more frequent doses. This treatment regime seems to be safe after 1 year of use as pharmacokinetic evaluation demonstrated a non-significant trend towards increased trough levels of drug concentration (76).

However, Christensen et al observed a significant increase of mesalazine and its main metabolite, N-acetyl-mesalazine, concentration in plasma on higher doses (77).

Nevertheless, we as clinicians have to remember that factors, such as patients´ understanding of the importance of treatment, adherence to 5-ASA and cost of the treatment could influence treatment efficacy.

Results (paper V)

Denmark

Out of 485 invited patients 233 patients were randomised; 117 to the web and 116 to the control group (fig. 8). The patients' description is presented in table 6. All of the web patients were competent with a self-initiated treatment and 88.8 % of web patients found the new system feasible and wanted to continue using it after end of the trial. At 12 months, only adherence to 4 weeks of acute treatment was statistically significant different between the web and the control groups; 73 % vs. 42 %; p=0.005 (fig. 9).

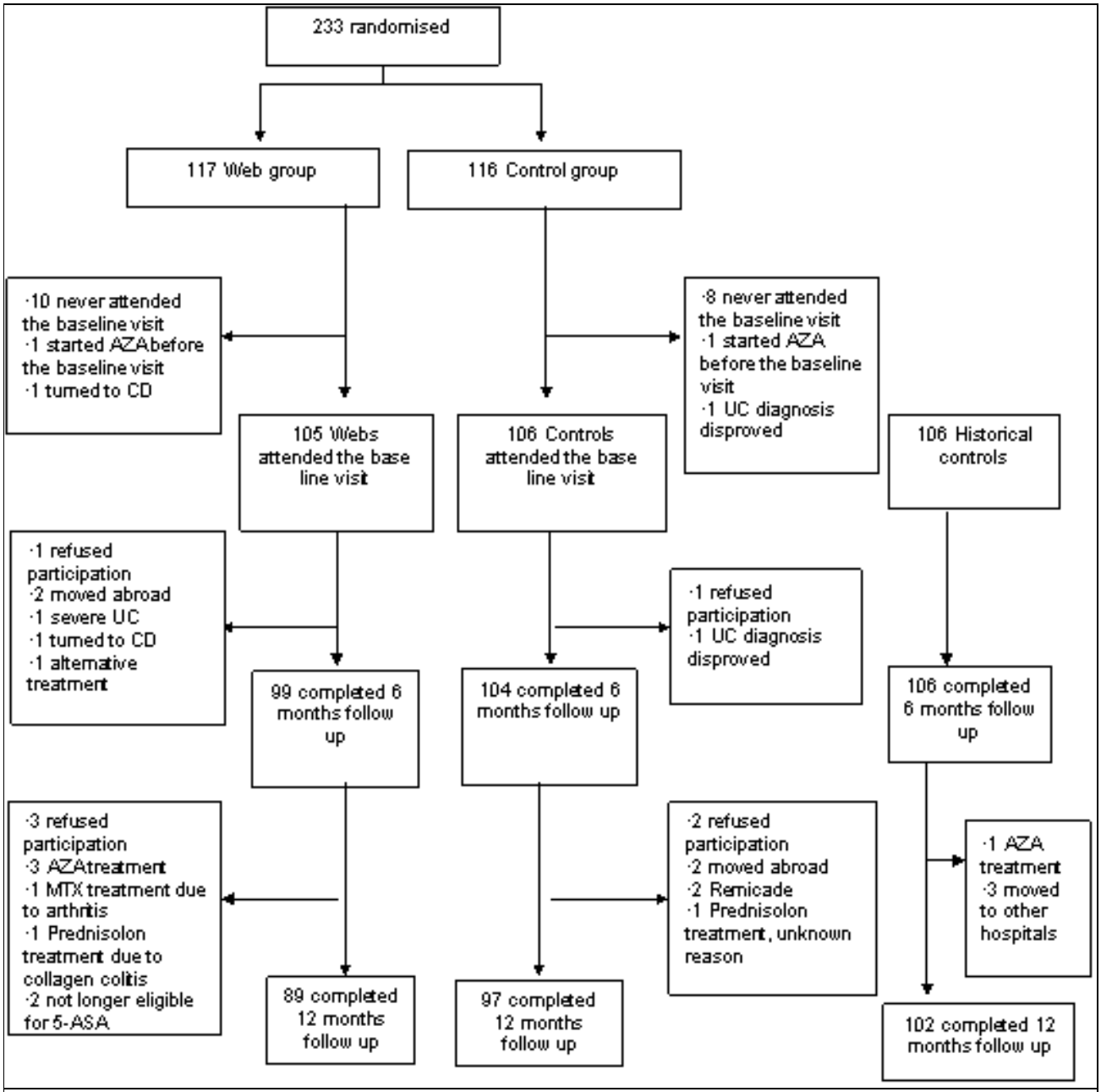

Figure 8
Study profiles of the randomised UC patients in Denmark in the web-based trial "Constant-care" (paper V) AZA= Azathioprine

PATIENTS AT RANDO-MISATION	WEB N=117	CONTROL N=116	P-VALUE	HISTORICAL CONTROL N=106
Gender Male, N (%) Female, N (%) Total	57 (48.7) 60 (51.3) 117	35 (30.2) 81 (69.8) 116	0.005	
Age at diagnosis Median (range)	33(3-66)	35 (14-65)	ns	
Age at inclusion Median (range)	41 (21-69)	48 (21-69)	0.01	
Disease duration, year Median (range)	4 (0-45)	6 (0-37)	ns	
Disease extension at diagnosis, N (%) Proctitis Left Sided Pancolitis	 31 (26.5) 60 (51.3) 26 (22.2)	 29 (25) 70 (60.3) 17 (14.7)	 ns	 53 (50.0) 36 (34.0) 17 (16.0)
PATIENTS AT BASE LINE	**WEB N=105**	**CONTROL N=106**		**HISTORICAL CONTROL N=106**
Gender Male, N (%) Female, N (%) Total	 52 (49.5) 53 (50.5) 105	 33 (31.1) 73 (68.9) 106	 0.008	 40 (37.7) 66 (62.3) 106
Age at diagnosis Median (range)	33 (3-66)	35 (14-65)	ns	32 (15-68)
Age at inclusion Median (range)	40 (21-69)	44 (21-69)	0.03	40 (18-69)
Disease duration, year Median (range)	4 (0-45)	6 (0-37)	ns	3 (0-42)
Disease extension, N (%) Proctitis Left Sided Pancolitis	 24 (22.9) 57 (54.3) 24 (22.9)	 25 (23.6) 67 (63.2) 14 (13.2)	 ns	 44 (41.5) 40 (37.7) 22 (20.8)
SCCAI Median (range)	1 (0-10)	1 (0-11)	ns	Not recorded
5-ASA treatment: Systemic, N (%) Asacol Pentasa Dipentum Premid Salazopyrin Mezavant None	 78 (74.3) 8 (7.6) 2 (1.9) 2 (1.9) 3 (2.9) 0 (0) 12 (11.4)	 68 (64.2) 7 (6.6) 4 (3.8) 2 (1.9) 6 (5.7) 0 (0) 19 (17.9)	 ns	 56 (52.8) 14 (13.2) 0 (0) 0 (0) 8 (7.5) 0 (0) 28 (26.4)
Topical, N (%) Suppositories Asacol Pentasa Mesasal Prednisolone None Enema/Foam Asacol Pentasa Colifoam Pred-Clysma None	 3 (2.9) 12 (11.4) 3 (2.9) 1 (1.0) 86 (81.9) 4 (3.8) 7 (6.7) 4 (3.8) 0 (0) 90 (85.7)	 2 (1.9) 9 (8.5) 1 (0.9) 0 (0) 94 (88.7) 4 (3.8) 6 (5.7) 4 (3.8) 0 (0) 92 (86.8)	 ns ns	 1 (0.9) 5 (4.7) 1 (0.9) 4 (3.8) 95 (89.6) 1 (0.9) 0 (0) 0 (0) 2 (1.9) 103 (97.2)

BMI Median (range)	24 (18-42)	24 (18-46)	ns	Not recorded
Smoking, N (%) Non-smoker Active smoker Ex-smoker	 39 (37.1) 19 (18.1) 47 (44.8)	 46 (43.4) 18 (17) 42 (39.6)	ns	Not recorded
Marriage status, N (%) Married Single	 69 (65.7) 36 (34.3)	 82 (77.4) 24 (22.6)	ns	Not recorded
Education, N (%) Academic Other education During education No education	 33 (31.4) 55 (52.4) 16 (15.2) 1 (1.0)	 29 (27.4) 64 (60.4) 5 (4.7) 8 (7.5)	ns	Not recorded
Occupation, N (%) Paid Unpaid Support Pensioner	 82 (77.1) 1 (1.0) 15 (14.3) 7 (6.7)	 86 (81.1) 4 (3.7) 6 (5.7) 10 (9.4)	ns	Not recorded

Table 6 Description of the Danish UC patients at randomisation and baseline visit in the web-based trial "Constant-care" (paper V)

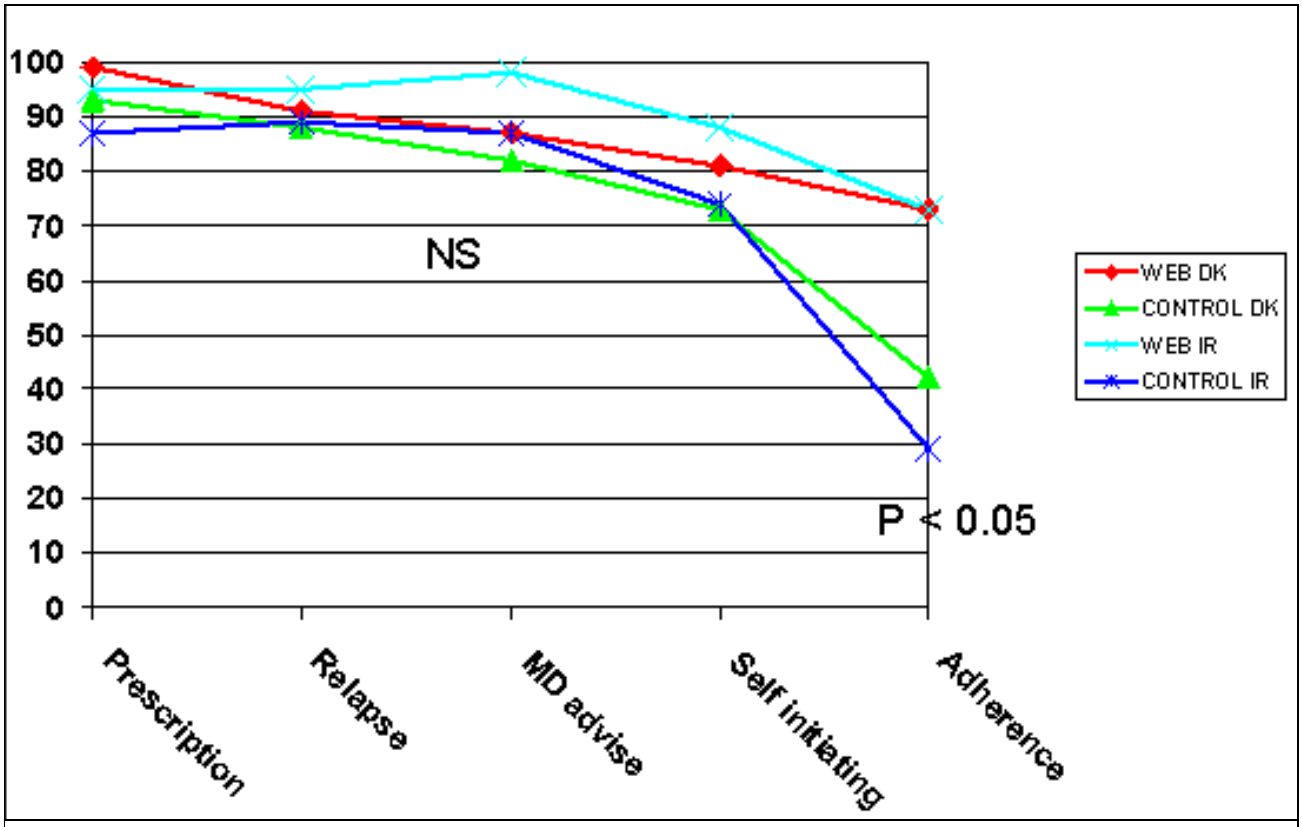

Figure 9
UC patients´ self-report of prescription, self-recognition of relapse, following doctor's advice, self-initiating of acute treatment and adherence to 4 weeks of acute 5-ASA therapy in Denmark and Ireland (paper **V**)

Community Effectiveness of the Constant-care approach consists of previously reported 80 % remission rate on combined 5-ASA treatment (15) multiplying with the outcome's preceding probabilities in the five compliance steps from the CQ (fig. 10).

Based on the e-prescription pharmacy database, 68 % of web vs. 69 % of control patients refilled ≥ 80 % of prescribed 5-ASA treatment during the study. At the end of the trial, 3 of 4 IBD knowledge items were significantly improved in web vs. control patients (Table 7).

The web-patients showed an improvement of the disease specific QoL, p=0.04, as well as general health, p=0.009, vitality, p=0.03, role emotional, p< 0.0001 and social functioning, p=0.002 compared to the control group. We did not detect any worsening of depression and anxiety in both groups.

As expected half of the patients experienced at least one relapse during the study. Web patients reported slightly more relapses, however this was not statistically significant, mean 1.1 (0-6) vs. 0.8 (0-4) in control group. Relapse duration in the web group were shorter than in the control group (median 18 days [95% CI 10-21] vs. 77 days [95% CI 46-108] days), p<0.001 (fig. 11).

When we compared acute systemic treatment with high doses of 5-ASA at relapse, the results showed that all (100 %) of web patients started this treatment as recommended by the program in contrast with 10 % of control patients, who followed the treatment regimes in the out-patient clinic, p<0.0001. Use of oral and topical 5-ASA treatment, number of days lost through illness, improvement of the disease activity (SCCAI ≤5), disease extension and hospitalisation did not show any significant difference between the groups. In total, we received 696 faecal samples for calprotectin measurement, whereof 43 samples from web and 32 samples from controls patients were received within 7 days of relapse and compared to the symptoms: bowel frequency day and/or night and/or blood in stool. We detected that 70 % of web vs. 78 % of control patients had FC value higher than 50 mg/kg at time they reported relapse symptoms.

No significant difference was observed in adverse events due to 5-ASA treatment. Moreover, none of the patients died, developed toxic megacolon, required colectomy or developed IBD related cancer during the study. This result was confirmed by data from the Danish death, surgery and cancer register.
In comparison we registered 86 acute visits due to UC symptoms and 57 routine visits to the outpatient clinic less in web vs. control patients, respectively, p<.0001.

Furthermore, during the study period we received 86 e-mails and 21 phone calls from web-patients vs. 7 e-mails and 17 phone calls from the control patients. Reduction of the visits, number of hospitalisation, e-mails and phone calls were converted into financial saving for our department during the 1 year trial period, which was 19,831 Euro for 105 patients, equivalent to 189 Euro/patient/year (Table 8).

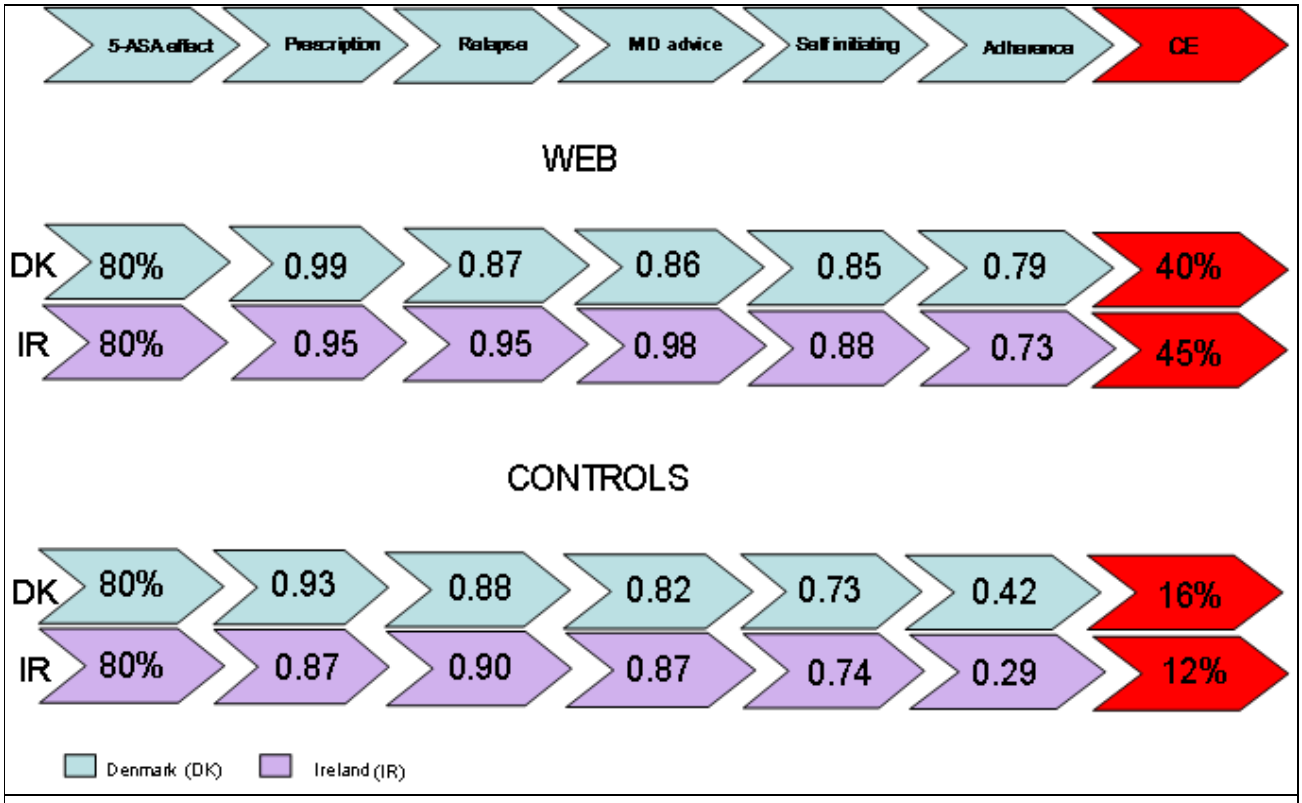

Figure 10
Community Effectiveness (CE) of the Constant-care approach after one year in Danish and Irish UC patients (paper V)

Grouping	Changing	Control N (%)	Web N (%)	P-value
General IBD understanding	Improved	37 (39)	68 (76)	<.0001
	Same	24 (25)	6 (7)	
	Worse	34 (36)	15 (17)	
	Total	95 (100)	89 (100)	
Medication	Improved	40 (42)	61 (69)	0.0007
	Same	34 (36)	21 (24)	
	Worse	21 (24)	7 (8)	
	Total	95 (100)	89 (100)	
Diet	Improved	28 (29)	20 (22)	0.1293
	Same	57 (60)	65 (73)	
	Worse	10 (11)	4 (4)	
	Total	95 (100)	89 (100)	
Complications of IBD	Improved	31 (33)	58 (65)	<.0001
	Same	53 (56)	23 (26)	
	Worse	11 (12)	8 (9)	
	Total	95 (100)	89 (100)	

Table 7
Improvement of the Danish UC patients´ inflammatory bowel disease specific knowledge (CCKNOW) at 12 months after education of the web group (paper V)

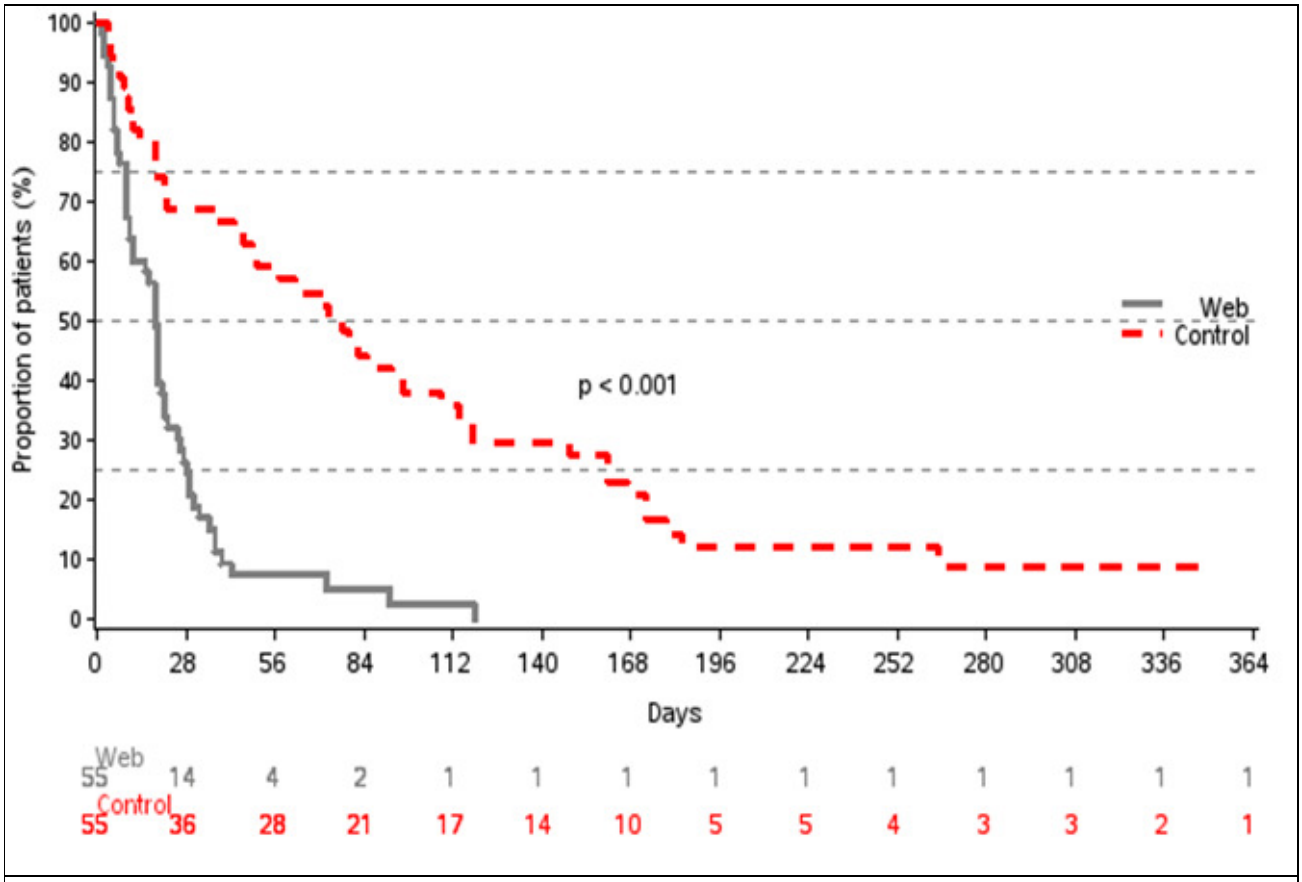

Figure 11
Time (days) from the first relapse to remission in Danish web and control UC patients during one year of follow-up. Median time in the web-group is 18 days vs. 77 days in the control-group (paper V)

	ALL OUTPATIENT VISITS 161 EURO/VISIT		HOSPITALISATION 2,601 EURO/HOSPIT		PHONE/ON LINE CONSULTATION 21 EURO/CONSULTATION	
	NUMBER	EURO	NUMBER	EURO	NUMBER	EURO
WEB	80	12,880	2	5,202	107	2,247
CONTROL	214	34,454	2	5,202	24	504
Difference: Control-web	21,574		0		-1,743	
TOTAL COST	19,831 Euro for 105 patients in study period = 189 Euro/patient/year					

Table 8
Economic cost of treatment of Danish web- and control patients. Price per visit, hospitalisation and phone consultation due to the Danish Disease Related Groups (DRG) tariff per 2009 transferred to Euro (paper V)

We also calculated the patients´ direct cost of actual systemic and local 5-ASA medication during the study period using the Defined Daily Dose, which resulted in 641 Euro/randomised patient for web vs. 578 Euro/randomised patients for control group.

The historical control group was comparable with the control group and helped us to confirm identical general clinical approach using for treatment and follow-up of the patients in out-patient clinics.

The overall influence of the "Constant-Care" approach on Danish patients after one year of study has been summarised (fig. 12).

1. Feasibility of using/potential use of the web-program
2. Following medical doctors advise at relapse
3. Adherence to 4 weeks of acute 5-ASA treatment
4. High dose of systemic 5-ASA at relapse
5. Inflammatory Bowel Diseases
6. Disease specific quality of life
7. Hospital Anxiety and Depression Scale
8. Time to remission ≤ 11 days at 1. relapse
9. Reduction of the disease activity (SCCAI ≤ 5)
10. Faecal calprotectin > 50 mg/kg
11. Compliance with systemic and topical 5-ASA treatment during the study (based on the e-prescription pharmacy database)

Ireland

In the Irish trial 100 patients were randomised; 52 to the web and 48 to the control group, whereof 51 and 41, respectively, attended the baseline visit, and 40 web and 38 control patients completed 12 months follow up. Only 15 patients denied participations due to following reasons: 1) do not participate in any research projects; 2) too many questionnaires; and 3) wish not to deal with any stool samples. 88 % of web patients found the new system feasible and wanted to use it in the future.

As in Denmark only the self-reported adherence to 4 weeks of acute treatment gave a statistically significant difference between the groups, 73 % vs. 29 %, respectively, p=0.03 (fig. 9). The Community Effectiveness of the Constant-care approach was 33 % higher in the web patients compared to controls (fig. 10).

Furthermore we found the following changes: Improvements in SF-12 of mental health, p=0.01, physical functioning, p=0.03, and social functioning, p=0. 02 in the web patients as well as an anxiety improvement in web patients, p=0.02. Only 39 % of web-patients and 24 % of control patients reported at least one relapse during the 12 months of study, which was unexpected. Relapse frequency in the web–group was higher (mean 0.6 (0-4)) compared to the control group (mean 0.2 (0-1)), p=0.02. However, relapse duration in the web-group was shorter than in the control group (observed median 30 (2-37) vs. 70 (7-217) days), p<0.03. Only 15 % of web and 10 % of control patients have been treated with high doses of systemic 5-ASA at time of relapse.

We received 99 faecal samples for FC measurement. However, the number of samples from the control patients received within 7 days of relapse was too small, and therefore made measurement of over treatment impossible.

We registrated 29 routine visits less to the outpatient clinic in web vs. control patients, p=0.007. In addition no significant difference was found between the two study groups in number of acute visits, improvement of IBD knowledge, disease specific QoL, depression score, number of days lost through illness, improvement of the disease activity, disease extension, hospitalization, adverse events, severe complications or mortality. The historical control group was similar to the randomised control group.

Discussion

In paper V we showed that the new web based approach "Constant-care" for UC patients with 5-ASA treatment was feasible in both Denmark and Ireland. Approximately 88 % of both Danish and Irish patients preferred this approach to conventional care. This result is corresponding well with the study by Robinson and colleagues, where 82 % of patients from the intervention group preferred to use the new guided self-management system (62). A similar result was reported by Cross et al, where 90 % of UC patients would agree to use home telemanagement in the future (78). Educated patients felt safe to follow the web-guided recommendation for the self-initiated 5-ASA treatment. One of the reasons for that was the close monitoring of patients by the web-doctors online. This result supported the fact that, all Danish web-patients were able to treat relapses themselves with high doses of systemic 5-ASA compared to only 10 % of control patients treated in the out-patient clinic. This difference can be explained. Many of our clinicians initiate Asacol at a dose of 3.2 mg/day in case of relapse and then increase the dose up to 4.8 mg/day for those patients who did not respond to lower doses during one month or more. The reason for this treatment strategy, in the clinical setting, has been discussed in paper IV, but it also could be a fear of the adverse events. However, in our study, we did not observe a statistical difference in occurrence of adverse events between the groups. This finding is in contrast with the result from the internet-based monitoring of asthma patients by Linda Rasmussen et al, where side-effects such as dysphonia and oropharyngeal candidiasis, were more common in the internet group, p<0.001(30).

At the end of the study, the web-group was significantly better adherent to 4 weeks of acute treatment than the control-group, the difference being 31 % in Denmark and 44 % in Ireland. Furthermore, we detected a better Community Effectiveness, being 24 % higher in the Danish and 33 % higher in the Irish web-group than in the respective control-groups. In Denmark, we observed the interesting fact that approximately 70 % of both web- and control patients refilled their prescribed 5-ASA medication. Despite this, duration of relapse in the web-group was shorter than in the control-group, the difference of 59 days. This finding supported our hypothesis that rapid start of sufficient systemic 5-ASA treatment is an important factor for improving the treatment outcome in UC patients.

Patient education is a major component of the web-based approach, and showed in Denmark a significant improvement of patients' general IBD knowledge and disease specific quality of life without increasing morbidity, depression and anxiety. Unfortunately, a similar improvement of general IBD knowledge could not be detected in the Irish patients.

As expected, 1/2 of Danish patients reported at least one relapse during the one year follow-up in contrast to Ireland, where frequents of relapses were lower. The reasons for that could be 1) lack of epidemiological studies, so we simply do not know the disease course in Ireland. For example, in a study by Kane the annual incidence of relapse for described UC patients was about 20 % (23); 2) lack of exchange of information between GPs´ and hospitals, as UC patients can be treated in primary care; and 3) lack of reporting of relapses by the patients. Moreover only 10 % of web and 15 % of control patients having a relapse used sufficient systemic 5-ASA treatment. A high price of the 5-ASA medica-

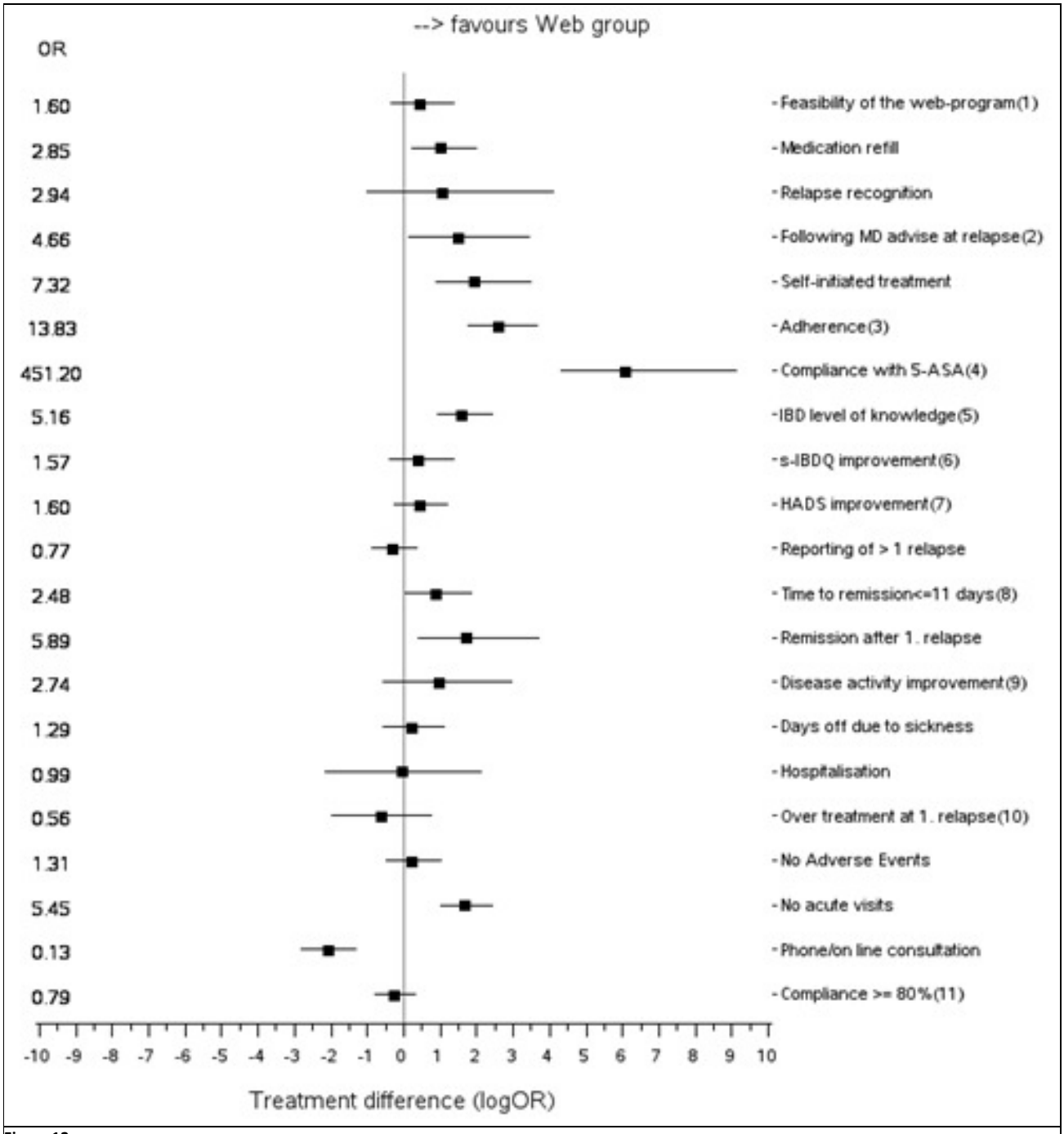

Figure 12
Influence of the "Constant-Care" approach on Danish patients after one year of study. Performance in web-group compared with performance in control group. Y-axis represents OR, X-axis represents logOR of the treatment difference (paper V)

tion could explain this fact. Even so, a shorter duration of relapse was observed in the web-group.

In 2/3 of the Danish web-patients, as well as control-patients, the relapse symptoms were confirmed by FC-test > 50 mg/kg. This indicated that the web-patients were not over-treated by high dose of systemic 5-ASA as compared with the treatment regimes in the out-patient clinic. Unfortunately, compliance with faecal samples during relapses was very low in Irish patients. We can speculate that the reasons for this outcome could be the study design as both investigators and the patients were blinded to the FC results and it lead to misunderstanding of this importance. It also could be due to reluctance of stool sampling.
The Danish web-patients made 86 acute outpatient visits less than control patients despite the reporting of slightly more relapses. This result is similar to the finding in a study by Robinson, where the patients from the interventional group made significantly fewer visits to the hospital and to the general practitioners than control patients, $p<0.006$ (62).

The design of our study resulted in more e-mails and phone calls from the web-patients than from the control patients. Despite this fact, the web-based self-management decreased treatment costs by 189 Euro per patient during one year of follow-up. However, we have to be critical regarding this finding as reduced number of visits did not change the actual working hours of the medical staff. Nevertheless, it seems to support our hypothesis that the web-based approach can be helpful in increase of consultation time for more severe patients without increase of waiting time for other patients in the out-patients clinic.

With regard to the differences in outcome measures between Denmark and Ireland we have to take into account variations between health care systems, standard treatment schemes for IBD patients in out-patients clinics and/or general practice, patients' mentality, and economical limitations. The new web-guided approach on www.constant-care.dk seems to be feasible, safe and cost-effective for UC patients at least in this RCT. Furthermore, the concept complies with the action plan for a European e-Health Area (28), which gives patients important opportunities for improved access to better and more efficient health care. But to support our results, a larger clinical set-up should be applied.

However, as our study is the first RCT within e-Health in IBD, it is important to discuss limitations of the web-based approach. The concept has been validated on a selected group of patients. It is obvious that not all IBD patients will be able or willing to switch from the standard care to a new one. Therefore further studies regarding the web-based treatment of more severe UC and Crohn disease are needed.

The web-program can be further improved by attaching a list of all possible adverse events (AE) of medication, and results of the blood tests. This information will be helpful for both patients and medical providers in prevention of eventual AE.

One of the biggest issues is acceptance and legalisation of the approach by the health care authorities, as it has been done for phone-consultations and phone "help-lines". Another barrier can be difficulties with its implementation as this process may require a reshaping of the current health care system and reorganisation of the out-patients clinics, which could be costly. However, we believe that in the long-term it would not only lead to savings in both time and costs, but what is more important, it will also provide a better quality of care to our patients.

ETHICAL CONSIDERATIONS

The study was approved by the Danish Ethical Committee (KA 05115) and Irish Ethical Committee of St James's Hospital and the Adelaide & Meath Hospital incorporating The National Children Hospital at Tallaght. All participating patients gave their informed consent. The studies did meet the requirements of the Danish Data Protection Agency.

A NEW RAPID HOME TEST FOR FAECAL CALPROTECTIN IN ULCERATIVE COLITIS (PAPER III)

Results

We analysed 404 faecal samples from UC patients participated in the RCT "Constant-Care". Both rapid tests showed acceptable agreement compared to the ELISA method. Mean differences in faecal calprotectin (mg/kg) for ELISA vs. Home Test (HT photo), ELISA vs. RT (scanning model) as well as RT (scanning model) vs. HT photo correlated with ELISA and each other significantly (r RT vs. ELISA= 0.954, $p < 0.001$, r HT vs. ELISA = 0.939, $p < 0.001$ and r RT vs. HT = 0.961, $p < 0.001$, respectively).

We found a good agreement between all three tests at a cut off level of 50 mg/kg calculated by kappa statistic: for ELISA vs. RT scanning 86 % (95 % CI, range 80 %-91 %), ELISA vs. HT photo 87 % (95 % CI, range 82 % - 91 %) and RT scanning vs. HT photo 95 % (95 % CI, range 92 %-98 %). Table 9 shows the sensitivity, specificity and predictive values for RT scanning and HT photo using a cut-off 50 mg/kg.

Assay	Parameter	Estimated 95% CI (range)
RT scanning	NPV	96.6 % (92.7 - 98.7)
	PPV	90.0 % (85.3 - 93.5)
	SENSITIVITY	97.2 % (93.9 - 99.0)
	SPECIFICITY	88.0 % (82.6 - 92.3)
HT photo	NPV	95.6 % (91.5 - 98.1)
	PPV	91.5 % (87.0 - 94.8)
	SENSITIVITY	96.2 % (92.7 - 98.4)
	SPECIFICITY	90.1 % (85.0 -93.9)

NPV = Negative Predictive Value, PPV = Positive Predictive Value

Table 9
Sensitivity, specificity and positive and negative predictive values for the Rapid Test (RT scanning) and Home Test (HT photo) compared with ELISA using cut-off values of 50 mg/kg (paper III)

Furthermore we detected an acceptable intra-patient coefficient of variation (CV %) for HTphoto 4.9 % (range, 0-141.4 %) compared with ELISA was 3.6 % (range, 0 -25.8 %), $p < 0.0003$. Assay reproducibility was comparable between the tests (ELISA 19.8 %, RT scanning 21.1 % and HT photo 24.5 %).

Discussion

In this study two completely new quantitative rapid lateral flow tests for FC measurement: scanning model (RT scanning) and home test via mobile phone (HTphoto) was described and validated. The HTphoto test showed both a good agreement of 87 % at a cut-off of 50 mg/kg, an acceptable CV of 4.9 %, and a significant correlation with ELISA and RT scanning.

We also found high sensitivity and specificity (96.2 % and 90.1 % respectively), as well as predictive values (NPV 95.6 % and PPV 91.5 %) compared with the "Gold Standard" ELISA. These numbers are generally higher than reported by Vestergaard et al (79) and can be explained by differences in the tests.

Moreover we observed a better correlation between the HT photo versus ELISA for FC values only up to 500 mg/kg. FC values above 500 mg/kg showed a high dispersion of the differences between all 3 tests. This inaccuracy could limit the test use. On the other hand in the clinical setting FC > 500 mg/kg will indicate an active disease requiring acute treatment. However, in the future correlation between FC measurement and the clinically and endoscopically disease severity will be necessary. We showed the similar result of assay reproducibility as previously described by Røseth et al, when 10 freshly made extracts from each faecal sample were tested by all three tests (48).

Our study has also limitations. The home test was performed by experienced biomedical laboratory technicians in order to assess the accuracy of the new methods. This result was a first step before initiation of a new trial in which the rapid test HT photo is performed by the patients at home. For this purpose home stirrers containing buffer have been developed, so the patients can easily use them for the FC measurement. Furthermore we made an informational DVD for the patients explaining how to use the rapid test at home.

While our earlier results from paper II showed that between 70 % and 100 % of the UC patients had no problem in doing stool sampling, it is obvious, that not all IBD patients may be capable or willing to perform of FC measurement at home. In this situation the RT scanning may be a more appropriate method for accurate measurement and receiving of the FC result within 24 hours.

Nevertheless, as clinicians we have to be aware of and recognise that FC is a non-specific, surrogate marker of inflammation and both false positive and false negative results may appear.

This fact can explain the clinical situations, when FC is above 50 mg/kg, but endoscopic picture by MAYO score is 0 and wise versa if FC less than 50 mg/kg with the MAYO score of I or II.
When all pros and cons are considered, we believe, that in the future properly educated and trained patients will be able to analyse FC and based on this initiate sufficient treatment at www.constant-care.dk, independently of hospitals working hours.

CONCLUSION AND PERSPECTIVES

Increasing incidence of UC, young age of the patients, and poor adherence with treatment have received attention during the past years. We conducted the ECCO consensus (paper I) regarding the IBD patients´ need for Quality of Health Care (QoHC). It has been concluded that evidence-based medicine in QoHC is limited throughout Europe. Furthermore optimisation of the QoHC in Europe is needed. This requires "information"; "education", "benchmarking", and "psychological analysis", which can help to improve patient compliance, increase Quality of Life, and decrease depression, and anxiety. We also proposed future aspects to optimise QoHC in IBD.

A new virtual approach for UC patients and 5-ASA treatment "Constant-Care", including the web-program www.constant-care.dk and the patient education centre (PEC), was presented and validated in a RCT (paper V). To our knowledge, the www.constant-care.dk is the first web-based 5-ASA treatment solution program for UC patients, where not only the health care providers, but also the patients can follow their disease history and be actively involved in the disease management. This RCT has shown that the "Constant-Care" approach seems to be feasible, safe and cost effective, at least on the selected group of the UC patients included in the trial. Ability to rapid start of sufficient 5-ASA treatment resulted in a decreased duration of relapse in the web patients. However, further studies in a larger clinical set-up are needed to support these results.

Furthermore, we also validated two completely new quantitative rapid tests for FC measurement to increase patients' possibility for relapse validation at home. Both tests: Scanning model (RT scanning) for laboratory use and home test for patient use (HTphoto) showed a significant correlation with the "Gold Standard" ELISA. We also found high sensitivity (97.2 % and 96.2 %) and specificity (88 % and 90.1 %), and high predictive values (NPV 96.6 %, 95.6 % and PPV 90 %, 91.5 %, respectively) compared with ELISA. We concluded that the new rapid tests seem to be reliable and might be an alternative to existing ELISA. However, future studies are needed to examine the feasibility of the home test performed by patients as part of the disease control and self-management.

Based on the results from the web-based concept, we have initiated two new studies. The first one is "Traffic light for Crohn patients (CD) and Remicade treatment", which includes both educational training of CD patients, web self-management of the symptoms, and FC measurement by rapid test scanning model during one year. All together it aims to optimise the treatment dosage, timing, and cessation of Remicade. The second study concerns "Web-based treatment in patients with Irritable bowel syndrome (IBS)". In this trial the patients are randomised into 3 groups: 1. Dicoflor (Lactobacillus rhamnosus) treatment, 2. Diet excluding fermentable saccharides and polyols (FODMAP), and 3. Control group for 6 weeks. FC is measured by ELISA.

The new web-based treatment approach "Constant-Care" complies with an action plan for a European e-Health Area, aiming at giving patients opportunities for improved access to better and more efficient health care. No doubt, a widespread implementation of "Constant Care" will require a reshaping of the current health care for IBD patients. However, we believe that future patients care will embrace this concept, which will empower patients in disease self-management, and hopefully also reduce their dependency on doctors.

SUMMARY

Ulcerative Colitis (UC) together with Crohn's disease (CD) belongs to inflammatory bowel diseases (IBD). IBD is to date as frequent as Insulin Dependent Diabetes (IDDM) and is second to Rheumatoid arthritis (RA) in its chronicity. The majority (91 %) of patients with UC have a mild to moderate disease course eligible for 5-ASA treatment. Poor adherence in UC is a well known phenomenon, which is associated with a 5-fold increased risk of relapse and increased health care costs. Web-based treatment solution with self-initiated 5-ASA treatment in UC based on the patient's pattern recognition of the disease course had not been published previously.

The aims of the thesis were: 1) In a European evidence based consensus to assess the IBD patients' need for Quality of Health Care (QoHC); 2) To validate the influence of a Patient Educational Center (PEC) and a web-based treatment solution program, www.constant-care.dk, on patients´ disease self-management, adherence, Quality of Life, and disease course after 1 year of self-initiated 5-ASA treatment. UC patients in a conventional out-patient setting were used as controls; 3) To validate two new quantitative rapid tests (RT scanning and HT photo) for Faecal Calprotectin (FC) measurement, and to assess whether HT photo can be useful as a home test to help the patients deciding on self-initiated treatment.

The ECCO Consensus found evidence for optimising QoHC by "information"; "education", "benchmarking", and "psychological analysis", which could help to improve patient compliance, QoL, and to decrease depression and anxiety. UC patients, educated in the PEC, significantly improved the level of disease specific knowledge. Patient education and training on www.constant-care.dk, being validated on first 21 Danish patients and subsequently on 233 Danish and 100 Irish patients, showed that the new web guided approach was feasible, safe, and cost effective for the selected group of the patients included in the trial. Use of the web concept increased patients adherence to acute 5-ASA treatment, ($p= 0.005$) and community effectiveness up to 33 %, improved Quality of Life, ($p= 0.004$), increased patients' ability to sufficient self-initiated treatment and reduce out-patient visits, ($p<0.0001$). Patients´ morbidity and depression remained unchanged. Median duration of relapse in the web-group was 59 days shorter than in the control-group possibly due to high dose of systemic 5-ASA treatment, ($p< 0.0001$).

We found that the new rapid home test (HT photo) was accurate and comparable with the Enzyme-linked immunosorbent assay (ELISA) with a 90 % specificity and a 96 % sensitivity. The rapid test can be useful in clinical settings concerning disease self–monitoring at home, which would decrease the use of endoscopy in some cases.

The findings corresponded well with action plan for a European e-Health Area and could be a helpful tool to provide more efficient health care for UC patients. Widespread implementation of the "Constant-Care" is possible, but it may require a reshaping of the current health care for IBD patients both legally and eco-

nomically. It may also empower patients in disease self-management and reduce dependency on doctors. Future long-term studies are needed to investigate, if this concept could possibly change the natural disease course.

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APPENDIX II

QUESTIONNAIRES

Compliance Questionnaire

1. Do you consider it easy for you to renew a prescription for your medicine? (E.g. Asacol, Dipentum, Pentasa)?

Yes **No**

If yes, do you renew it through: Your GP (general practitioner)

The outpatient department

"Constant-Care"?

2. Are you able to recognise a relapse of the disease?

Yes **No**

3. Do you follow your doctor's recommendations regarding medical treatment?

During relapse **Yes** **No**

During remission **Yes** **No**

4. When experiencing a relapse, are you able to initiate the medical treatment on your own?

Yes **No**

5. When experiencing a relapse, do you apply the recommended dosage of tablets, suppositories or enemas?

Yes **No**

If yes, do you apply it for: **4 weeks**

2- 3 weeks

1- 2 weeks

< 1 week

If no, do you apply: **80 %** of dosage

50 % of dosage

< 50 % of dosage

Nothing at all

Constant *Care*

Satisfaction (CONTROL patients)

VAS - VISUEL ANALOG SCALE (10cm line)

1. If you get the possibility, in case of relapse, to treat yourself from home by a special developed computer program, which can guide you in treatment with 5-ASA (f. ex Asacol, Dipentum, Pentasa), would you make use of it?

Not at all **Very much**

---

2. Would you like to have the possibility to be educated in Ulcerative colitis, treatment etc in our Patient Educational Center (PEC) in the future?

Not at all **Very much**

---

3. How important has the project" Constant-Care" been to you?

Not at all **Very much**

---

4. Do you think that" Constant-Care" has changed your quality of life?

Worsen **Improved**

---

5. Do you think that your disease course has been changed during the last 12 months?

Worsen **Improved**

Constant *Care*

Satisfaction (WEB patients)

VAS - VISUEL ANALOG SCALE (10cm line)

1. Would you like to have the possibility to use the web-program "Constant-Care" in the future?
   Not at all **Very much**

   _____

2. Would you like to have the possibility for continuously education in our Patient Educational Center (PEC) in the future?
   Not at all **Very much**

   _____

3. How important has the project "Constant-Care" been to you?
   Not at all **Very much**

   _____

4. Are you more uncertain due to self-initiated treatment after the education in the PEC?
   Not at all **Very much**

   _____

5. Do you feel more depressed after the education in the PEC?
   Not at all **Very much**

   _____

6. Do you think that "Constant-Care" has changed your quality of life?
   Worsen **Improved**

   _____

7. Do you think that your disease course has been changed during the last 12 months?
   Worsen **Improved**

   _____

8. Did you use the E-learning program often?
   Not at all **Very much**

   _____

Constant *Care*

Disease activity index SCCAI

Please, choose one answer for every question from 1 to 5

1. Bowel frequency (day)

1-3
4-6
7-8
> 9

2. Bowel frequency (night)

None
1-3
4-6

3. Urgency of defecation

None
Urgency
Immediately
Incontinent

4. Blood in stool

None
Trace
Occasionally frank
Usually frank

5. General well being

Very well
Slightly below par
Poor
Very poor
Terrible

6. Extra intestinal manifestations

Inflamed or painful joints (arthritis)
Inflamed eyes (iritis, uveitis)
Tender, red nodules under the skin
(Erythema nodosum)
Blister, red bumps or ulcers on legs and/or arms
(Pyoderma gangrenosum)

S-INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (S-IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been. On this questionnaire there are 32 questions. Each question has a graded response numbered from 1 through 7. Please read each question carefully and answer the number which best describes how you have been feeling in the past 2 weeks.

1. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the past 2 weeks? Please choose an option from:
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

2. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from:
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

3. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from:
A great deal of difficulty; activities made impossible
A lot of difficulty
A fair bit of difficulty
Some difficulty
A little difficulty
Hardly any difficulty
No difficulty; The bowel problems did not limit sports or leisure activities

4. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from:
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

5. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from:
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

6. Overall, in the last 2 weeks, how much of a problem have you with passing large amounts of gas? Please choose an option from:
A major problem
A big problem
A significant problem
Some trouble
A little trouble
Hardly any trouble
No trouble

7. Overall, in the last 2 weeks, how much of a problem have you had maintaining, or getting to, the weight you would like to be at? Please choose an option from:
A major problem
A big problem
A significant problem
Some trouble
A little trouble
Hardly any trouble
No trouble

8. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from:
1. None of the time
2. A little of the time
3. Some of the time
4. A good bit of the time
5. Most of the time
6. Almost all of the time
7. All of the time

9. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from:
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

10. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from:
1. All of the time
2. Most of the time
3. A good bit of the time
4. Some of the time
5. A little of the time
6. Hardly any of the time
7. None of the time

TESTING YOUR KNOWLEDGE OF CROHN'S AND COLITIS: THE CCKNOW SCORE

This questionnaire will help your doctors and nurses know on which topics you may need more information. This will help make your treatment more effective. Please tick only one answer for each question. Thank you.

1. The intestines play an important role in the body but they only work during meal times:
a) True
b) False
c) Don't know

2. People with inflammatory bowel disease are never allowed to eat dairy products:
a) True
b) False
c) Don't know

3. Elemental feeds are sometimes used to treat Crohn's disease and ulcerative colitis. They:
a) Always contain a lot of fibre
b) Are very easy to digest
c) Come in the form of tablets
d) Don't know

4. Proctitis:
a) Is a form of colitis that affects the rectum or back passage only
b) Is a form of colitis that affects the whole of the large bowel
c) Don't know

5. When a patient with inflammatory bowel disease passes blood in their stool it means:
a) They definitely have bowel cancer
b) They are having a flare up of their disease
c) Don't know

6. Patients with inflammatory bowel disease are probably cured if they have been symptom free for 3 years:
a) True
b) False
c) Don't know

7. Inflammatory bowel disease runs in families:
a) True
b) False
c) Don't know

8. If patients with inflammatory bowel disease are not careful with their personal hygiene they can pass on their disease to friends and members of the family:
a) True
b) False
c) Don't know

9. Patients with inflammatory bowel disease can get inflammation in other parts of the body as well as the bowel:
a) True
b) False
c) Don't know

10. A fistula:
a) Is an abnormal track between 2 pieces of bowel or between the bowel and skin
b) Is a narrowing of the bowel which may obstruct the passage of the contents
c) Don't know

11. The terminal ileum:
a) Is a section of the bowel just before the anus
b) Is a section of the bowel just before the large intestine
c) Don't know

12. During a flare up of inflammatory bowel disease:
a) The platelet count in the blood rises
b) The albumin level in the blood rises
c) The white cell count in the blood falls
d) Don't know

13. Steroids (such as prednisolone/prednisone/budesonide/hydrocortisone):
a) Can only be taken by mouth
b) Can be given in the form of an enema into the back passage
c) Cannot be given directly into the vein
d) Don't know

14. Steroids usually cause side effects:
a) Only after they have been taken for a long time and in high doses
b) Immediately and even after small doses
c) Which are not permanent and all disappear after treatment is stopped
d) Don't know

15. Immunosuppressive drugs are given to inflammatory bowel disease patients to:
a) Prevent infection in the bowel by bacteria
b) Reduce inflammation in the bowel
c) Don't know

16. Sulphasalazine:
a) Controls the level of sulphur in the bloodstream
b) Can be used to reduce the frequency of flare ups
c) Cannot be used to prevent flare ups
d) Don't know

17. An example of an immunosuppressive drug used in inflammatory bowel disease is:
a) Sulphasalazine
b) Mesalazine
c) Azathioprine
d) Don't know

18. If a woman has Crohn's disease:
a) She may find it more difficult to become pregnant
b) She should not have children
c) Her pregnancy will always have complications
d) She should stop all medication during her pregnancy
e) Don't know

19. Patients who smoke are more likely to have:
a) Ulcerative colitis
b) Crohn's disease
c) Don't know

20. Which one of the following statements is false?
a) Ulcerative colitis can occur at any age
b) Stress and emotional events are linked with the onset of ulcerative colitis
c) Ulcerative colitis is least common in Europeans and North Americans
d) Patients with ulcerative colitis have an increased risk of developing bowel cancer
e) Don't know

21. The examination of the large bowel with a flexible camera is called a:
a) Barium enema
b) Biopsy
c) Colonoscopy
d) Don't know

22. Male patients who take sulphasalazine:
a) Have reduced fertility levels that are reversible
b) Have reduced fertility levels that are not reversible
c) The drug does not have any effect on male fertility
d) Don't know

23. The length of the small bowel is approximately:
a) 2 feet
b) 12 feet
c) 20 feet
d) Don't know

24. The function of the large bowel is to absorb:
a) Vitamins
b) Minerals
c) Water
d) Don't know

25. Another name for an ileorectal anastomosis operation with formation of a reservoir is:
a) Purse
b) Pouch
c) Stoma
d) Don't know

26. If a part of the bowel called the terminal ileum is removed during surgery the patient will have impaired absorption of:
a) Vitamin C
b) Vitamin A
c) Vitamin B12
d) Don't know

27. Patients with IBD need to be screened for cancer of the colon. Which one of the following statements about screening is false? Screening should be offered to all patients with ulcerative colitis:
a) Which affects only the rectum
b) Which has lasted for 8–10 years
c) Which started before the age of 50
d) Don't know

28. There are millions of tiny "hairs" in the small bowel to increase the absorptive surface. They are called:
a) Villi
b) Enzymes
c) Bile salts
d) Crypts
e) Don't know

29. Which one of the following is not a common symptom of inflammatory bowel disease?
a) Abdominal pain
b) Change in bowel habit
c) Headache
d) Fever
e) Don't know

30. If a child has inflammatory bowel disease; he/she probably will not:
a) Live beyond the age of 45
b) Be as tall as his or her friends
c) Be as intelligent as his or her friends
d) Don't know

SF- 36-Item Health Survey Questionnaire

This questionnaire is designed to find out your perception of your health. The information given will give an idea about, how well you are able to handle daily functions.
Answer each question by circling the answer which fits you best. If you are having trouble understanding a question, stop for a moment, think about what the question means to you. Then answer the question as best as you can.

1. In general, would you say your health is:	
Excellent	1
Very good	2
Good	3
Fair	4
Poor	5

2. Compared to one year ago, **how would your rate your health in general now?**	
Much better now than one year ago	1
Somewhat better now than one year ago	2
About the same	3
Somewhat worse now than one year ago	4
Much worse now than one year ago	5

The following items are about activities you might do during a typical day.
Does **your health now limit you** in these activities? If so, how much?
(Circle One Number on Each Line)

	Yes, Limited a Lot	Yes, Limited a Little	No, Not limited at All
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	[1]	[2]	[3]
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	[1]	[2]	[3]
5. Lifting or carrying groceries	[1]	[2]	[3]
6. Climbing **several** flights of stairs	[1]	[2]	[3]
7. Climbing **one** flight of stairs	[1]	[2]	[3]
8. Bending, kneeling, or stooping	[1]	[2]	[3]
9. Walking **more than a mile**	[1]	[2]	[3]
10. Walking **several blocks**	[1]	[2]	[3]
11. Walking **one block**	[1]	[2]	[3]
12. Bathing or dressing yourself	[1]	[2]	[3]

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?
(Circle One Number on Each Line)

	Yes	No
13. Cut down the amount of time you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks,** have you had any of the following problems with your work or other
regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(Circle One Number on Each Line)

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks,** to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?
(Circle One Number)

Not at all	1
Slightly	2
Moderately	3
Quite a bit	4
Extremely	5

21. How much **bodily** pain have you had during the **past 4 weeks**?
(Circle One Number)

None	1
Very mild	2
Mild	3
Moderate	4
Severe	5
Very severe	6

22. During the **past 4 weeks,** how much did **pain** interfere with your normal work (including both work outside the home and housework)?
(Circle One Number)

Not at all	1
A little bit	2
Moderately	3
Quite a bit	4
Extremely	5

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.
How much of the time during the **past 4 weeks** . . .
(Circle One Number on Each Line)

	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt down-hearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6

32. During the **past 4 weeks,** how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?
(Circle One Number)

All of the time	1
Most of the time	2
Some of the time	3
A little of the time	4
None of the time	5

How TRUE or FALSE is <u>each</u> of the following statements for you.
(Circle One Number on Each Line)

	Definitely True	Mostly True	Don't Know	Mostly False	Definitely False
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

SF- 12 A Quality of Life Questionnaire

This questionnaire is designed to find out your perception of your health. The information given will give an idea about, how well you are able to handle daily functions.

Answer each question by circling the answer which fits you best. If you are having trouble understanding a question, stop for a moment, think about what the question means to you. Then answer the question as best as you can.

1. How do you perceive your health, in general?

Excellent	1
Very well	2
Well	3
Less than good	4
Not good	5

The following questions deal with daily activities. Are you limited due to your health by any of these activities? And if so, to which extent?

	Yes, Very limited	Yes, Quite limited	No, Not limited at all
2. **Moderate activities**, such as: moving a table, vacuum cleaning, or bicycling	1	2	3
3. Walking up **several** flights af stairs	1	2	3

How often during the last 4 weeks, have you had any of the following problems with your work or other daily activities due to your physical health?

	Yes	No
4. I have decreased the amount of time I use at work or doing other activities	1	2
5. I have achieved less than I would have liked to	1	2

How often during the last 4 weeks, have you had any of the following problems with work or other daily activities due to emotional problems

	Yes	No
6. I have achieved less than I would have liked to	1	2
7. I have not done my work or activities as carefully as I usually do	1	2

8. To what extent has your physical pain affected your daily work(job and /or household),within the last 4 weeks?

Not at all	1
A little	2
Somewhat	3
Quite a lot	4
Very much	5

These questions deal with how you have been feeling during the last 4 weeks.

How much of the time within the last 4 weeks have you felt:

	All the time	Most of the time	Quite a lot of the time	Some times	Rarely	Never
9. Very nervous	1	2	3	4	5	6
10. Calm and relaxed	1	2	3	4	5	6
11. Depressed	1	2	3	4	5	6
12. Happy and satisfied	1	2	3	4	5	6
13. Worn out	1	2	3	4	5	6

Hospital Anxiety and Depression Scale (HADS)

This questionnaire is designed to help your doctor know how you feel. Read each item and place a firm tick in the box opposite the reply which comes closest to how you have been feeling in the past week. Don't take too long over your replies: your immediate reaction to each item will probably be more accurate than a long thought out response.

I feel tense or 'wound up':	**A**	**I feel as if I am slowed down:**	**D**
Most of the time	3	Nearly all of the time	3
A lot of the time	2	Very often	2
Time to time, occasionally	1	Sometimes	1
Not at all	0	Not at all	0

I still enjoy the things I used to enjoy:	**D**	**I get a sort of frightened feeling like 'butterflies in the stomach':**	**A**
Definitely as much	0	Not at all	0
Not quite so much	1	Occasionally	1
Only a little	2	Quite often	2
Not at all	3	Very often	3

I get a sort of frightened feeling like something awful is about to happen:	**A**	**I have lost interest in my appearance:**	**D**	
Very definitely and quite badly	3	Definitely	3	
Yes, but not too badly	2	I don't take as much care as I should	2	
A little, but it doesn't worry me	1	I may not take quite as much care	1	

Not at all		0	I take just as much care as ever	0	
I can laugh and see the funny side of things:	**D**		**I feel restless as if I have to be on the move:**		**A**
As much as I always could	0		Very much indeed		3
Not quite so much now	1		Quite a lot		2
Definitely not so much now	2		Not very much		1
Not al all	3		Not at all		0
				D	
Worrying thoughts go through my mind:		**A**	**I look forward with enjoyment to things:**		
A great deal of the time		3	A much as I ever did	0	
A lot of the time		2	Rather less than I used to	1	
From time to time but not too often		1	Definitely less than I used to	3	
Only occasionally		0	Hardly at all	2	
I feel cheerful:	**D**		**I get sudden feelings of panic:**		**A**
Not at all	3		Very often indeed		3
Not often	2		Quite often		2
Sometimes	1		Not very often		1
Most of the time	0		Not at all		0
I can sit at ease and feel relaxed:		**A**	**I can enjoy a good book or radio or TV programme:**	**D**	
Definitely		0	Often	0	
Usually		1	Sometimes	1	
Not often		2	Not often	2	
Not at all		3	Very seldom	3	