EHealth: Self-management in Inflammatory Bowel Disease and in Irritable Bowel Syndrome using novel Constant-Care Web Applications

Ehealth by constant-care in IBD and IBS

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LIST OF MANUSCRIPTS
This PhD thesis is based on the following four papers (three published and one submitted), which are referred to in the text as: CD study (I), UC study (II), IBS study (III) and IBD IBS-like symptoms study (IV).

Study I
Pedersen N, Elkjaer M, Duricova D et al. EHealth: Individualisation of Infliximab treatment and disease course via a self-managed web-based solution in Crohn's disease. Aliment Pharmacol Ther 2012. Nov; 36 (9):840-9.

Study II
Pedersen N, Thielsen P, Martinsen L et al. EHealth: Individualisation of Mesalazine treatment and optimization of disease course via a self-managed web-based solution in mild-to-moderate active Ulcerative colitis. Inflamm Bowel Dis 2014 Dec; 20 (12): 2276-85.

Study III
Pedersen N, Andersen N, Végh Z et al. Ehealth: Low FODMAP diet vs Lactobacillus Rhamnosus GG in Irritable Bowel Syndrome. World J Gastroenterol 2014. Nov; 20 (43):16215-16226.

Study IV
Pedersen N, Ankersen D, Felding M et al. Low FODMAP diet reduces irritable bowel symptoms and improves quality of life in patients with inflammatory bowel disease. Submitted.

1. INTRODUCTION

Inflammatory bowel diseases (IBD) such as Crohn's disease (CD) and ulcerative colitis (UC) are chronic inflammatory disorders affecting the gastrointestinal tract (1). The incidence and prevalence of IBD is increasing and a North-South and West-East gradient occurs, with the highest incidences found in Western and Northern Europe and North America (2-5). The peak age-interval at diagnosis is 16-35 years and approximately 6-7% percent of newly diagnosed patients are children below 15 years of age (6). Despite long-term intensive research, the exact etiopathogenesis of IBD is still unknown. The most widely accepted theory suggests that the disease results from a pathological interaction between the immune system and bacterial intestinal flora in an individual with a certain genetic predisposition (7). The disease is medically incurable and the goal of current therapy is to induce and maintain long-standing remission (8). The disease courses are characterised by periods of remission alternating with episodes of active disease of various length, frequency and severity (9-14). Although several clinical, genetic and serological markers have been identified to predict individual disease course, their use in daily clinical practice is limited and the disease evolution remains more or less unpredictable (3).

Infliximab (IFX), a chimeric monoclonal antibody against pro-inflammatory cytokine, tumor necrosis factor α (TNFα), has been proven to be effective in both CD and UC for both induction and maintenance therapy (15;16). IFX maintenance therapy is labeled every eight weeks (Q8W) as a way of preventing relapse, the formation of antibodies to IFX, and drug-related infusion reactions (15;17;18). However, when IFX is infused at regular Q8 intervals, inter-patient variation of pharmacokinetics, fluctuation in disease activity, and various phenotypes are not taken into account.

Traditional 5-aminosalicilic (5-ASA) preparations used in UC are effective in inducing and maintaining remission (19-22). However, these preparations have no mechanism for prolonging the release of 5-ASA in the colon, resulting in reduced availability in the left colon and a need for additional, rectally-administered treatment in some patients (22). Compliance is poor when the medication is administrated in different formulations and needs to be taken many times a day; non-compliance is an important reason for poor disease outcome (e.g. hospitalisations, colectomy) (23-26). Mesalazine with multi-matrix (MMX) system technology possesses a double matrix, allowing targeted and extended drug release

that is distributed through the entire colon and thus administered alone, once daily, and reduces the need for topical treatment (27-32). MMX formulation has proven to be an effective treatment of UC, optimising disease course and adherence to medication (30-32).

Irritable bowel syndrome (IBS) is a chronic functional gastrointestinal disorder characterized by intermittent abdominal pain or discomfort, associated with alterations in bowel habits and no findings of organic disease, of uncertain multifactorial aetiopathophysiology (33;34). It is a prevalent disorder affecting 10-20% of adolescents and adults in general population, with a higher prevalence in women and is associated with impaired quality of life, work productivity and increased economic burden for the healthcare system (35-41). Approximately 60-80% of patients with IBD in remission suffer from irritable IBS-like symptoms such as increased abdominal pain, bloating, distention and stool alteration (42-49). Medication used for IBS has been shown to be insufficient in reducing IBS symptoms in many patients (50;51). Different diets have been shown to influence IBS symptoms; however the benefits of these diets remain unproven (52;53). Recently, a diet rich in FODMAPs (Fermentable, Oligosaccharides, Disaccharides, Monosaccharides and Polyols) has been shown to be associated with worsening of IBS-like symptoms (34;54;55). The mechanism of FODMAPs inducing IBS-like symptoms is based on deterioration of the intestinal permeability (absorption) and activation of bacterial fermentation, increasing H_2 and CH_4 gas formation in the intestines (54-57). On the other hand, a diet low in FODMAPs (Low FODMAP diet, LFD) has been shown to reduce symptoms in IBS patients (58;59). More recently it has been shown in an Australian population that a LFD improve abdominal symptoms in IBD patients with IBS (60).

IBD is a disease of various manifestations regarding disease localisation, occurrence of complications and frequency of relapses (11). As such, different behaviour patterns and disease courses have been identified that classify patients into several subtypes (8;12). EHealth has the potential to turn these epidemiological disease patterns into individualised therapies, thereby increasing patient empowerment and compliance with treatment (61;62). As the diseases affect young people in their reproductive and productive years, an individual approach to the follow-up and treatment of this population is crucial. Pattern recognition of the disease course in IBD allows for the introduction of new and individually-tailored monitoring and treatment approaches to IBD (61;63-65) and for conditions related to IBD (e.g. irritable bowel syndrome, IBS).

Currently, the self-monitoring of disease activity (symptoms) occurs across many chronic conditions, including diabetes, chronic obstructive pulmonary disease (COPD) and heart diseases (66-76). This approach may lead to a quicker contacting of medical care providers in order to initiate treatment, thus reducing the frequency of the exacerbations of chronic conditions and improve disease course and quality of life.

In gastroenterology, the utilisation and efficacy of psychological eHealth Internet-based interventions have mostly been developed in functional bowel disorders, including IBS (77) and have been shown to reduce the severity of IBS symptoms and improve quality of life (78-81). So far, the evidence regarding eHealth approaches in IBD is limited but promising, both in UC (61;82;83) and in CD (62;84).

A previous thesis performed by our group was one of the first eHealth thesis based on the Constant-care concept – comprised of both a web-monitoring and web-treatment application – in patients with UC (85). The thesis showed that the eHealth approach improved adherence to medication, reducing time to remission and resulting in a better disease outcome and QoL, and that the approach was both feasible and cost-effective. However, the implementation and use of eHealth approaches remains limited; as such, there is a need for more research and experience in this field.

In this thesis we further extend eHealth approaches based on the Constant-care concept in specific IBD subgroups that may help individualise the monitoring and treatment of IBD and in patients with IBS. We examined whether the disease course, disease outcome, and quality of life could be improved by addressing patient education, adherence to medication, and access to care providers, the eHealth as a screening method for those at risk of early relapse.

2. AIMS

The primary aim of this thesis was to evaluate the efficacy and feasibility of novel Constant-care approaches in patients with IBD and IBS, in order to individualise their disease management.

Table 1. *The design of the studies presented in the thesis*

Study N	Study design	Population	Treatment	Control group	Web-intervention*	Study period
I	Open label	CD moderate-to-severe activity	Infliximab	Historic control	Monitoring Treatment	2009-2010
II	Open label	UC mild-to-moderate activity	Multimatrix Mesalazine	None	Monitoring Treatment	2012-2013
III	Randomised unblinded	IBS patients	Low FODMAP Diet	Normal Diet LGG	Monitoring	2009-2013
IV	Randomised unblinded	IBD patients with IBS	Low FODMAP Diet	Normal Diet	Monitoring	2012-2013

*CD: Crohn's disease; UC: ulcerative colitis; LGG: Lactobacilus Rhamnosus LGG. * All patients were involved in self-management on web.*

Furthermore, we assessed patients' quality of life, adherence, safety, satisfaction and costs using these web-applications. In particular we studied eHealth approaches in the following situations:

CD patients treated with IFX

UC patients treated with mesalazine

IBS patients and IBD patients with IBS symptoms treated with a Low FODMAP Diet.

3. MATERIAL & METHODS

DESIGN OF THE STUDIES

The design of the studies is described in Table 1.

Web-based applications

Studies were based on self-managed and web-guided applications: www.cd.constant-care.dk (Figure 1a), www.meza.constant-care.dk (Figure 1b) and www.ibs.constant-care.dk (Figure 1c). These are secure web-based applications that were developed by Prof. Pia Munkholm et al (86) and that consist of two principal components: a patients' registry and a monitoring or treatment element. The registry component is based on the Inflammatory Burden (IB) and IBS symptom severity system (IBS-SSS), while the web-guide part directs patients to register their symptoms and to take their medications or to contact the hospital.

After receiving a disease-specific education and theoretical/practical training in how to use the web application at the Patient Education Centre, each patient received an individual username and password from the investigators for accessing the application. The web applications were accessible from computers, laptops, tablets and smartphones. Furthermore, SMS text/e-mail information services were designed to guide patients with the monitoring of the symptoms and for treatment advice. The educational part of the website was covered by the eLearning and educational video-clips displaying information about the website, study medication and the study conditions. The administrator part of the web application, accessible only to the investigators, allowed the treating physician to monitor the patients. A disease activity status, measured by specific clinical indices, appeared on both the patient and administrator parts of the web application in the form of a simple 'traffic light' (TL) system: red indicated high disease activity, yellow moderate activity, and green indicated quiescent disease. In certain applications this status was supplemented with graphs on patients' faecal calprotectin (FC) and quality of life.

Disease activity by Inflammatory Burden on the web

Inflammatory Burden (IB) was a measure specifically created for the assessment of disease activity in patients with CD and UC in a web-treatment concept, consisting of a clinical index, Harvey-Bradshaw Index (HBI) or simple clinical colitis activity index (SCCAI) (87;88) and a biological marker, FC (89-96) (Figure 1a+1b). FC level in the stool was collected by patients using a home-administered collecting kit and subsequently sent to the research laboratory at the Gastroenterology Unit, Herlev University Hospital by post and analysed immediately by a quantitative enzyme immunoassay (CALPRO calprotectin ELISA) test on Dynex DS2 Magellan. Cut-off values of <200 (92;97) µg/g and <100 (90;98) were defined as remission in CD and UC.

Disease severity by IBS-SSS on the web

Severity of IBS symptoms was assessed by an international validated questionnaire, the IBS symptom severity system (IBS-SSS) (99), incorporated in the IBS application to be used by IBS and IBD patients for registering IBS-like symptoms. IBS-SSS evaluates the intensity of IBS symptoms on a five-item visual analogue scale (VAS) during the preceding 10 days and focusing on abdominal pain, distention, stool frequency and consistency, as well as interference with life in general. Each of the five subscores generates a maximum score of 100, which gives a maximum total score of 500. A higher score indicates more severe symptoms. A minimum of a 50-point reduction in IBS-SSS during the study was considered an improvement (60). The disease severity appears on the application as a TL colour score system (Figure 1c): Green = quiescent or mild symptom severity (0-175 points), yellow = moderate (175-300), red = severe (>300).
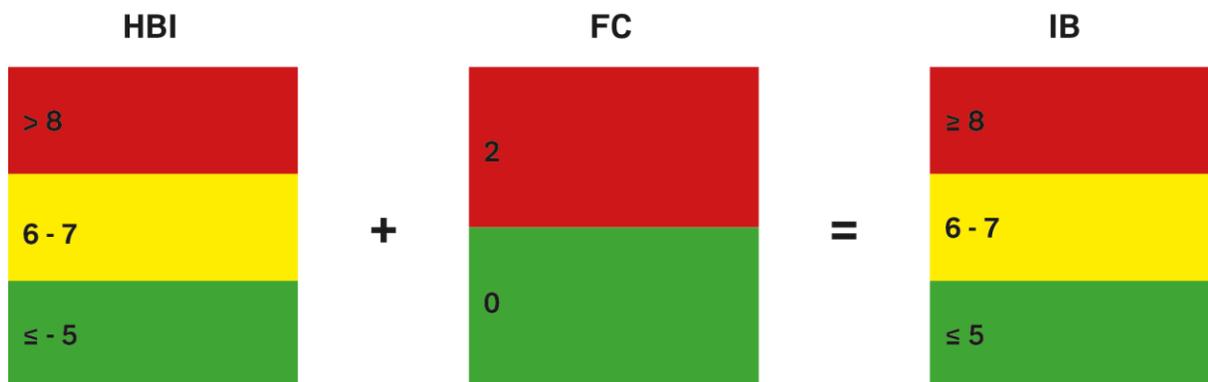

Figure 1a. *Concept of www.cd.constant-care.dk, a self-managed web-monitoring and web-treatment application in patients with Crohn's disease. Patients' assessment of disease activity by inflammatory burden (IB), a 'traffic light' colour score system using the Harvey-Bradshaw Index (HBI) and faecal calprotectin (FC): green = no activity, yellow = moderate activity, red = severe activity. Faecal calprotectin, µg/g: <200=0 points; ≥ 200=2 points.*
Web-treatment guide:
Green: No IFX infusions are recommended. Infusion at week 12 is recommended.
Yellow: Contact Day-Care for the infusion.
Red: Contact Day-Care for the infusion. Call study doctor.

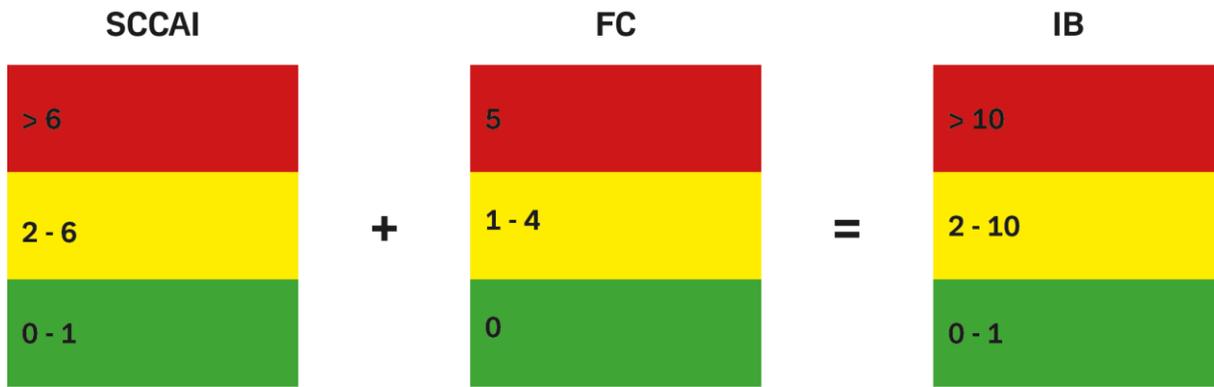|	SCCAI		FC		IB
	> 6		5		> 10
	2 - 6	**+**	1 - 4	**=**	2 - 10
	0 - 1		0		0 - 1

Figure 1b. *Concept of www.meza.constant-care.dk, a self-managed web-monitoring and web-treatment application in patients with ulcerative colitis. Patients' assessment of disease activity by inflammatory burden (IB), a 'traffic light' colour score system using the simple clinical colitis index (SCCAI) and faecal calprotectin (FC).*
Green = no activity, yellow = moderate activity, red = severe activity.
FC µg/g: ≤ 100=0 points; >100-400=1-4 points; ≥500=5 points (severe activity, red).
Web-treatment-guide:
Green: Reduce to 2-mesalazine tablets/day. Check again next week.
Yellow: Take 4-mesalazine tablets/day. Check again next week.
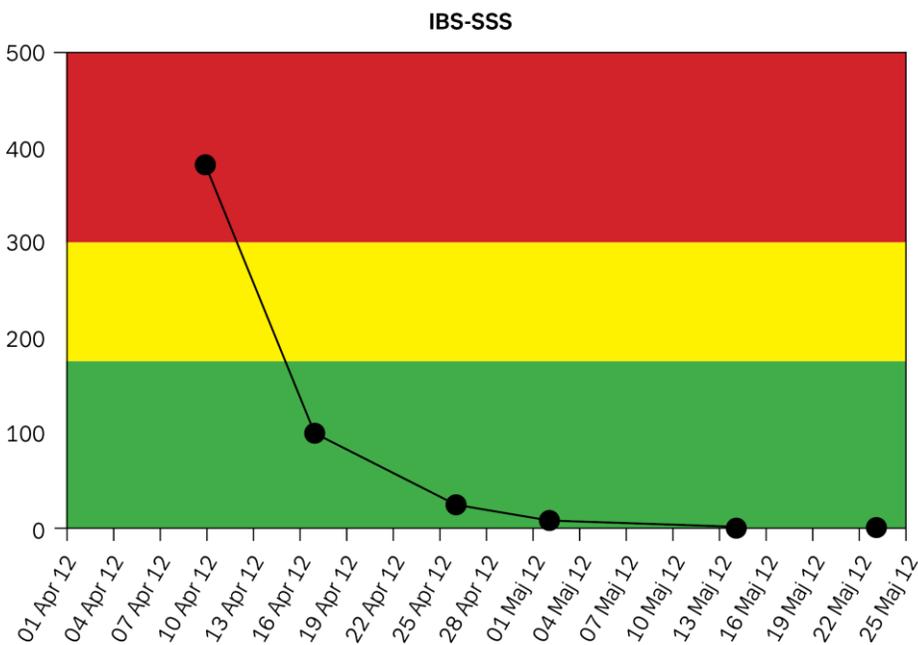*Red: Take 4-mesalazine tablets/day. Call study doctor.*

Figure 1c. *Concept of www.ibs.constant-care.dk, a self-managed web-monitoring application of the severity of irritable bowel syndrome (IBS).*
Patients' assessment of disease severity by web-registry of IBS-symptom severity system (IBS-SSS), a 'traffic light' colour score system. Green = quiescent or mild symptom severity; yellow = moderate symptom severity; red = severe symptoms.
IBS-SSS total score ranges from 0-500 points. Green=0-175 points; yellow=175-300; red>300.

STUDY PROCEDURES
Although all studies used web-based approaches in patient management, particular web-applications differed based on clinical situations.

Web-treatment with IFX
One month after each infusion, the patient and web-physician entered HBI and FC scores, respectively, into the web page on a weekly basis, allowing the application to calculate the IB and to

illustrate this via a TL system. As long as the IB score was in the green zone, indicating inactive disease, no infusion was given. If the IB exceeded the values denoted by the yellow or red zones, the application recommended that the patients contacted the day-care hospital, and their next IFX infusion was scheduled within 72 hours (Figure 1a).

Web-treatment with mesalazine
SCCAI and FC were entered weekly in the same manner as for CD patients on IFX. If the IB score was in the inactive green zone, the recommended mesalazine treatment dose was 2.4 g/day. If the IB exceeded the values denoted by the yellow zone, the application advised patients to increase the dose to 4.8 g/day. When IB reached the red zone, the application recommended that the patients contacted the day-care hospital, while continuing to take 4.8 g/day (Figure 1b).

Web-monitoring of IBS
IBS-SSS and IBS-QOL were entered weekly by IBD and IBS patients during a six-week trial. The application served as a kind of diary in which IBS symptoms were registered and it enabled the patients to monitor the severity of their symptoms. The application shows the patients their disease severity status and guides them through the missing registrations. No treatment guides were incorporated into the IBS application.

Additional questionnaires
The Short Inflammatory Bowel Disease Questionnaire (SIBDQ) (100) is an IBD-specific quality of life survey (10 questions with seven possible answers) covering four items (bowel, systemic, emotional and social). The results range from 10 (worst health) to 70 (best health). Good quality of life was considered as a score above 50 points.

The Short Form 12/36 (101;102) is a generic quality of life survey, covering eight items (Physical Functioning, PF; Role limitation due to Physical health, RP; Body pain, BP; General Health, GH; Vitality, VT; Social Functioning, SF; Role limitations due to Emotional problems, RE and Mental Health, MH) which are generalised as physical (PSC) and mental (MSC) health measures. The results are expressed on a scoring scale of 0-100 for every profile, with a mean health of 50 for the Danish population (101).

IBS-quality of life (IBS-QOL) is an IBS-specific quality of life survey (34 questions, five possible answers), covering eight items. The results range from 34 (best health) to 170 (worst health), transformed into a 0-100 scale, with higher scores indicating better IBS quality of life (103;104).

Adherence to the web-based registrations in both CD and UC was measured by the difference between the number of required registrations and the number of completed registrations per patient during the study period.

Adherence to medication in UC was measured using a Visual Analogue Scale (VAS) (23;105) and by Medical Adherence Rating Scale (MARS). VAS is a one-item 0-to-10 scale with 10 indicating full adherence (100%) and <8 (80%) as nonadherence. MARS is a five-item score on a Likert scale with a maximum score of 25; nonadherence was considered as <20.

Adherence to LFD in IBD patients with IBS-like symptoms was measured by the Food Frequency Questionnaire (FFQ) (106). It contains lists of the most commonly consumed high FODMAP foods adapted to the Danish population from Australian lists (106-108). Patients' FFQ was used to calculate the total quantity of FODMAP (g/day) intake for each patient.

Satisfaction with the web treatment was assessed in CD and UC patients using a self-developed questionnaire (6-items) on a VAS-score at the end of the study. An answer of more than 50% or more was considered a good level of satisfaction.

The cost of web treatment in the CD study was measured by total costs of the IFX infusions per patient per year via the web versus the cost of the IFX infusions via an outpatient clinic. In the UC study, the costs were calculated according to the cost of mesalazine (per day), web-treatment (per week) ± faecal calprotectin per patient (per week).

STATISTICAL ANALYSIS
Standard descriptive statistical analyses were performed, including frequency distributions, for categorical data and calculations of means (SD) or medians (range) for continuous variables. The Wilcoxon Signed-Rank test was used to compare variables of interest between baseline and end of follow-up. Mann-Whitney test was used to compare the outcomes between two different groups. Chi-square test and Student's t-test were used when appropriate for a comparison of baseline characteristics between patients and controls. A significance level of 5% was chosen.

The time to remission was analysed by using a multivariate Cox-proportional hazards regression model using the following covariates: gender, age, smoking status, UC location, duration, education, employment status, and baseline scores.

Multivariate logistic regression analysis was used to evaluate the impact of the following factors on change/response of the total IBS-SSS: age of 40 years, BMI, diagnosis, gender, IBD duration of 5 years, smoking, prior surgery, IBD maintenance therapy (5-ASA, thiopurines and biologicals) and disease activity.

The data from these Constant-care databases were directly exported to the statistician for statistical analysis and in this way blinded for the investigators.

All data were processed with SPSS software Version 19 &20 for Windows (SPSS Inc., Chicago, IL) and SAS software version 9.3 (SAS Institute Inc. Care. NC. USA).

ETHICS
All other studies were approved by the Danish Ethical Committee (Study I: KA 05115/13768; Study II: H-2-2011-129; Study III: H-2-2011-095-IBS; Study IV: H-2-2012-05/3898).

4. RESULTS
EFFICACY AND FEASIBILITY OF WEB-TREATMENT APPROACHES

Web-treatment with IFX in CD
A total of 27 consecutive patients with moderate-to-severe CD treated with IFX maintenance therapy were initially included in the study. Four patients were later excluded from the analysis due to protocol violations: nonadherence (n=2), planning of pregnancy (n=1) and urgent bowel resection (n=1). Of the 23 patients analysed 17 (74%) completed the entire 52 week period and 6 (26%) patients completed at least a 26-week period of follow-up online according to the protocol. Furthermore, 69 CD patients from the same participating centres treated by traditional approaches during the same period as the web patients (± 0.5 years) served as a historical control.
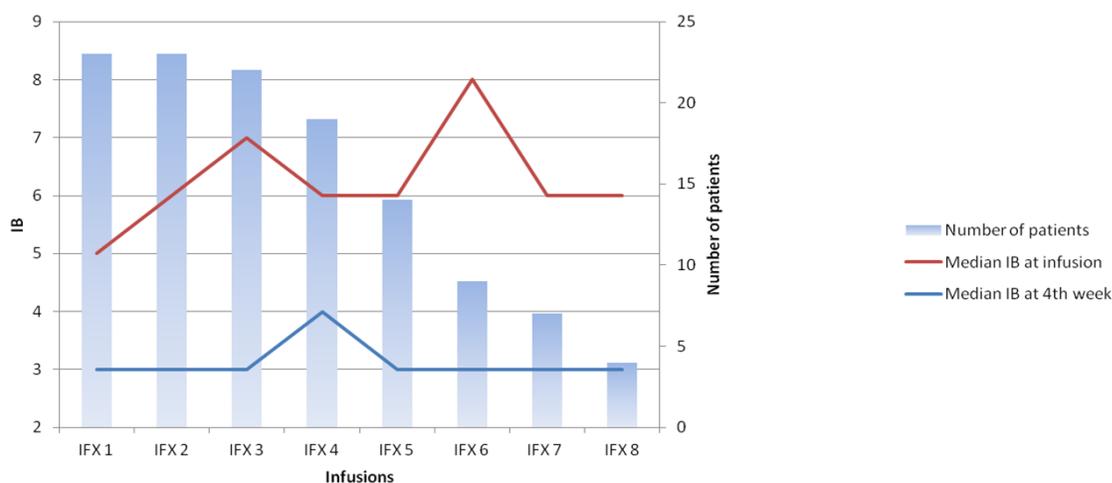
Figure 2. *Inflammatory burden (IB) at infliximab (IFX) infusion and four weeks after infusion as measured on the website*
X-axis: Ranking of infusions from first to eighth from inclusion until end of the study
Y-axis: Scoring of IB: ≤5 no activity; 6-7 moderate activity and ≥8 severe activity
Red line: IB levels indicating need for infusion
Blue line: Patients' response to IFX therapy 4 weeks after infusion

IFX treatment
In the web group, a total of 121 IFX infusions at a dose 5 mg/kg weight were given with a median interval of Q9W (range 4-18) and a median number of 5 (range 2-8) IFX infusions per patient. Twelve (10%) infusions were given at Q8W intervals, 49 (40%) at<Q8W and 60 (50%) at intervals of >Q8W. Fourteen patients (61%) had a mean interval between infusions >8 weeks, 3 (13%) <8 weeks and 6 (26%) patients had exactly 8 weeks.
In the control group, a total of 420 IFX infusions were given with a median interval of Q8W (range 4-16) and a median number of 7 (range 3-12) infusions per patient. Twenty-seven patients (39%) had a mean interval between infusions >8 weeks, 25 (36%) <8 weeks and 17 (25%) patients had exactly 8 weeks. No statistically significant differences in mean interval between IFX infusions comparing controls and web patients was observed (p=0.18).

Figure 2 illustrates the median IB per infusion during web-treatment. No statistically significant difference in IB was observed between baseline and end of study (mean 2.4 vs 2.2, p=0.4).

Web-treatment with mesalazine in UC
A total of 95 consecutive UC patients with mild-to-moderately active disease who were on maintenance oral or topical 5-ASA were recruited and switched to high (4.8 g/day) MMX mesalazine monotherapy, once daily, for the induction of the remission. Thirteen (14%) patients were excluded shortly after initiation due to nonadherence (n=12) and pregnancy (n=1). The final study population comprised the remaining 82 UC patients.

Disease activity
Overall, 72 (88%) patients were responders (IB ≤1, green and yellow zone) and 10 (12%) non-responders (IB>10, red zone) requiring rescue therapy with steroids, azathioprine and biologicals. The median time to initiation of the rescue therapy was 50 days (range 30-90). Of responders, 65 (90%) experienced remission on mesalazine as monotherapy (complete responders), while 7 (10%) were partial responders and needed additional topical 5-ASA preparations within median of 25 (20-35) days from the beginning of the study.
There was a statistically significant reduction of SCCAI, FC and IB from week 0 to week 12 in all patients (mean SCCAI: 4.6±1.9 vs 1.6±2.0, p>0.001; mean FC: 437±568 vs 195±385, p<0.001 and mean IB: 6.7±3.2 vs 2.4±3.2, p<0.001, Figure 3a, 3b, 3c).
Cox regression analysis (Table 2) of remission in SCCAI and IB changes during 12 weeks showed that UC patients with short disease duration (≤5 years) responded significantly more poorly compared to those with longer disease duration. Patients with a non-academic education were more likely to be in remission than patients with an academic education, while females were less likely to experience an SCCAI response to mesalazine therapy than males.
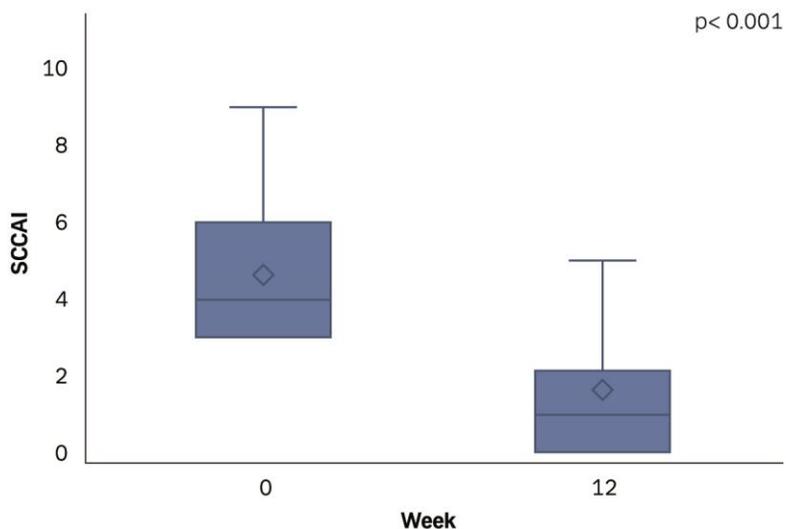
Figure 3a. *Box plot of simple clinical colitis activity index (SCCAI) (means/quartiles/range) score changes from baseline to week 12 of the study period in patients with ulcerative colitis treated with mesalazine.*

Figure 3b. *Box plot of faecal calprotectin (FCµg/g) (means/quartiles/range) changes from baseline to week 12 of the study period in patients with ulcerative colitis treated with mesalazine.*

Figure 3c. *Box plot of inflammatory burden (IB) (means/quartiles/range) score changes from baseline to week 12 of the study period in patients with ulcerative colitis treated with mesalazine.*
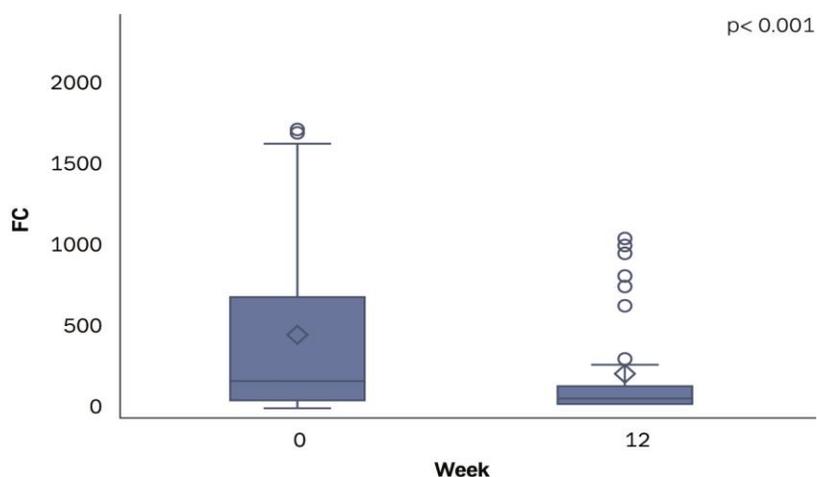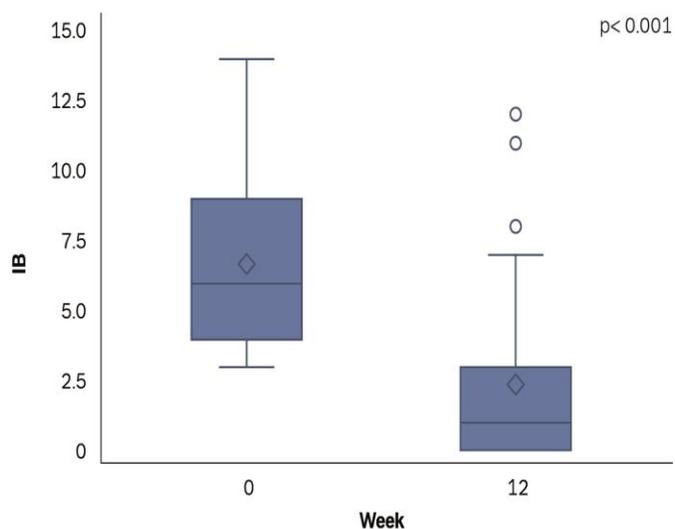
Table 2. *Factors influencing time to SCCAI remission (SCCAI≤1), FC remission (FC=0) and IB remission (IB ≤1) by multivariate proportional Hazards Model (Cox regression).*

Risk factor for SCCAI remission	HR (95% CI)	p
Baseline SCCAI (per SCCAI point)	0.63 (0.51-0.77)	<0.001*
Age (≤35 years)	1.72 (0.78-3.83)	0.18
Disease duration (≤5 years)	0.26 (0.13-0.51)	<0.001*
Smoking (current vs never)	2.77 (0.94-8.19)	0.07
Gender (female vs male)	0.42 (0.24-0.77)	<0.01*
Location (E1 vs E2)	0.62 (0.34-1.12)	0.11
Education (non-academic vs academic)	2.74 (1.31-5.74)	<0.01*
Employment (no vs yes)	1.27 (0.66-2.44)	0.48
Risk factor for FC score remission		
Baseline FC (per 100 FC units)	0.88 (0.83-0.94)	<0.001*
Age (≤35 years)	0.98 (0.46-2.07)	0.95
Disease duration (≤5 years)	1.49 (0.83-2.68)	0.18
Smoking (current vs never)	0.95 (0.35-2.56)	0.91
Gender (female vs male)	1.46 (0.86-2.50)	0.16
Location (E1 vs E2)	0.93 (0.54-1.61)	0. 80
Education (non-academic vs academic)	0.96 (0.48-1.93)	0.91
Employment (no vs yes)	0.89 (0.50-1.57)	0.68
Risk factor for IB remission		
Baseline IB (per IB point)	0.82 (0.74-0.91)	<0.001*
Age (≤35 years)	1.77 (0.76-4.15)	0.19
Disease duration (≤5 years)	0.30 (0.15-0.60)	<0.001*
Smoking (current vs never)	2.79 (0.87-8.96)	0.09
Gender (female vs male)	0.60 (0.33-1.09)	0.09
Location (E1 vs E2)	1.27 (0.71-2.30)	0.42
Education (non-academic vs academic)	2.20 (1.02-4.73)	0.45
Employment (no vs yes)	1.39 (0.75-2.599	0.30

*Note: Faecal calprotectin (FC): 0 score points=≤100 µg/g; IB: inflammatory burden score; SCCAI: simple clinical colitis activity index; E1: proctitis; E2: left-sided colitis; FC: faecal calprotectin; * statistically significant results*

A Kaplan-Meier curve (Figure 4) for time to SCCAI, FC and IB remission illustrates that 50% of patients achieved SCCAI remission at week 4, FC remission (FC<100 µg/g faces) at week 1 and a IB remission at week 6.

Based on IB remission values the dose of mesalazine was reduced to 2.4 g in 25% of patients at week 3, in 50% of subjects at week 6, and in 88% of patients at week 12.

Web-monitoring of IBS
In the IBS study, a total of 123 patients with IBS, fulfilling Rome III diagnostic criteria (38;109) were randomized to LFD (n=42), to LGG (n=41) and to the ND (n=40).

In the IBD study, a total of 89 IBD patients – 61 (69%) with UC and 28 (21%) with CD – were consecutively recruited into the study and randomized to LFD (n=44) and ND (n=45). Patients were in remission (87%) or with mild-to-moderate disease activity (13%) and had IBS-like symptoms based on Rome III diagnostic criteria for IBS.
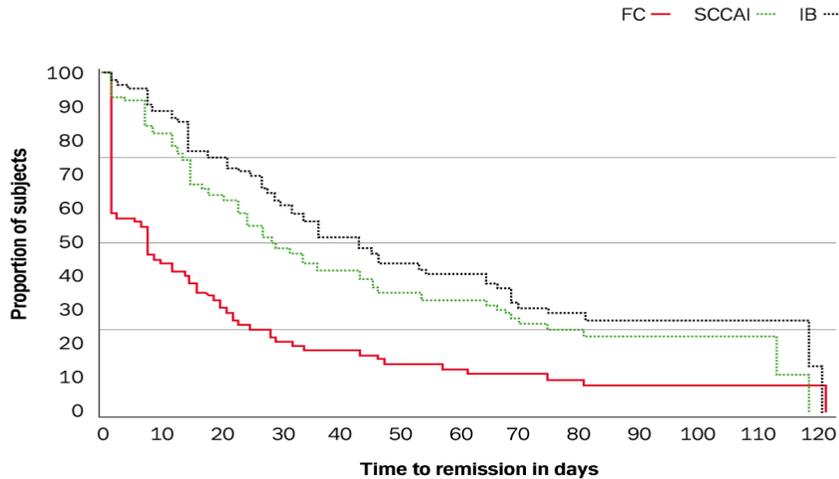
Figure 4. *Kaplan-Meier curve of time to simple clinical colitis activity index (SCCAI) remission (SCCAI ≤1), time to faecal calprotectin (FC) remission (FC ≤100 μg/g faeces), and time to inflammatory burden (IB) remission (IB ≤1) in patients with ulcerative colitis treated with mesalazine during 12 weeks*

Disease severity

Overall, in the IBS study there was a significant reduction of mean ± SD IBS-SSS in all patients from baseline to week 6 (mean±SD=308±88 vs 230±121, p<0.01), as well as in each treatment group: LFD (mean 327±93 vs 194±123, p<0.001), LGG (279±84 vs 211±118, p<0.01) and ND (318±83 vs 285±107, p<0.01).

At week 6, a statistically significant reduction in the mean±SD in IBS-SSS was observed in LFD (133±121) and LGG (68±106) groups compared to the ND group, (34±94) p<0.01.

In the IBD study, a total of 30 (81%) patients were responders (IBS-SSS reduction) in LFD group and 19 (46%) in ND, p<0.01. The response rates in overall IBS-SSS and its subscores in IBD patients are illustrated in Table 3.

Overall, there was a significant reduction of IBS-SSS in all patients from baseline to week 6 (mean score 243 vs 152, p<0.001) as well as in each treatment group: LFD (232±79 vs 119±105, p<0.001)

and ND (249±99 vs 181±118, p<0.01) (Figure 5). A significantly greater reduction in IBS-SSS was observed in the LFD group as compared to the ND group (mean score -114±96 vs -68±95, p = 0.02, Figure 5). Adjusted for baseline measures, logistic regression analysis identified treatment LFD/ND (Odds ratio (OR) 5.3; 95% CI: 1.8-15.6, p<0.01) as clearly associated with the overall IBS-SSS response (Table 4)

QUALITY OF LIFE

The mean SIBDQ in web-based treatment with IFX in CD patients did not change significantly between baseline and end of study (55 vs 55, p=0.73, Figure 6). Likewise, generic quality of life measured by SF-36 showed no statistically significant difference when comparing mean values of each item: PF (95 vs 95, p=0.66), RP (75 vs 87, p=0.75), RE (100 vs 100, p= 0.07), BP (84 vs 84, p=0.43), MH (76 vs 74, p=0.53), VT (60 vs 75, p=0.36), SF (87 vs 100, p=0.72), and GH (52 vs 49, p=0.86).

Table 3. *Response rates of overall IBS-SSS and subscores in IBD patients, LFD vs ND*

IBS-SSS N (%)	Overall	Pain intensity	Pain duration	Abdominal distension	Stool frequency & consistency	Interference with life
LFD	30 (81)	18 (49)	25 (68)	28 (76)	23 (62)	25 (68)
ND	19 (46)	16 (39)	18 (44)	29 (71)	16 (39)	25 (61)
P#	<0.01*	0.30	0.03*	0.52	0.06	0.44

IBD: inflammatory bowel disease. IBS: irritable bowel syndrome. SSS: symptom severity system.
*=statistically significant results. #p-values derived from logistic regression analysis of response rates.

Table 4. *Impact factors on the IBS-SSS overall response in patients with IBD*

Factor	OR	Lower	Upper	p-value
IBS-SSS baseline	1.00	0.99	1.00	0.33
IBD duration ≤5 years	0.39	0.14	1.11	0.08
LFD vs ND	5.29	1.81	15.6	<0.01*

*IBD: inflammatory bowel disease. IBS: irritable bowel syndrome. SSS: symptom severity score; OR (Odds Ratio). LFD: low FODMAP diet, ND: normal Danish/Western diet. * Statistically significant results*

In web-based treatment with mesalazine in UC patients, a significant improvement in total SIBDQ scores and subscores from baseline to end of study was observed (mean SIBDQ 47 vs 58, p<0.001, Figure 7) as well as in SF-12 summary scores MSC (mean 218 vs 248, p<0.01) and PSC (mean 226 vs 253, p<0.01). Similarly, statistically significant improvement in SIBDQ was observed in IBD patients treated with LFD compared to the ND group (mean SIBDQ dif. 9.1 vs 0.9, p <0.001, Figure 8).
No statistically significant improvement in IBS-QOL was observed when comparing LFD and ND groups in IBS cohort and IBD patient's cohort at the end of the study.

ADHERENCE
Adherence to the web applications/registrations was satisfactory in both CD and UC studies. In CD, adherence to the web registrations was 86% (with 534 weeks registered by patients compared to 624 weeks recommended by application). Deviation from protocol requirements regarding infusion interval was observed in 16 (13%) of IFX infusions, which were given after an interval of 12 weeks (13-18 weeks).
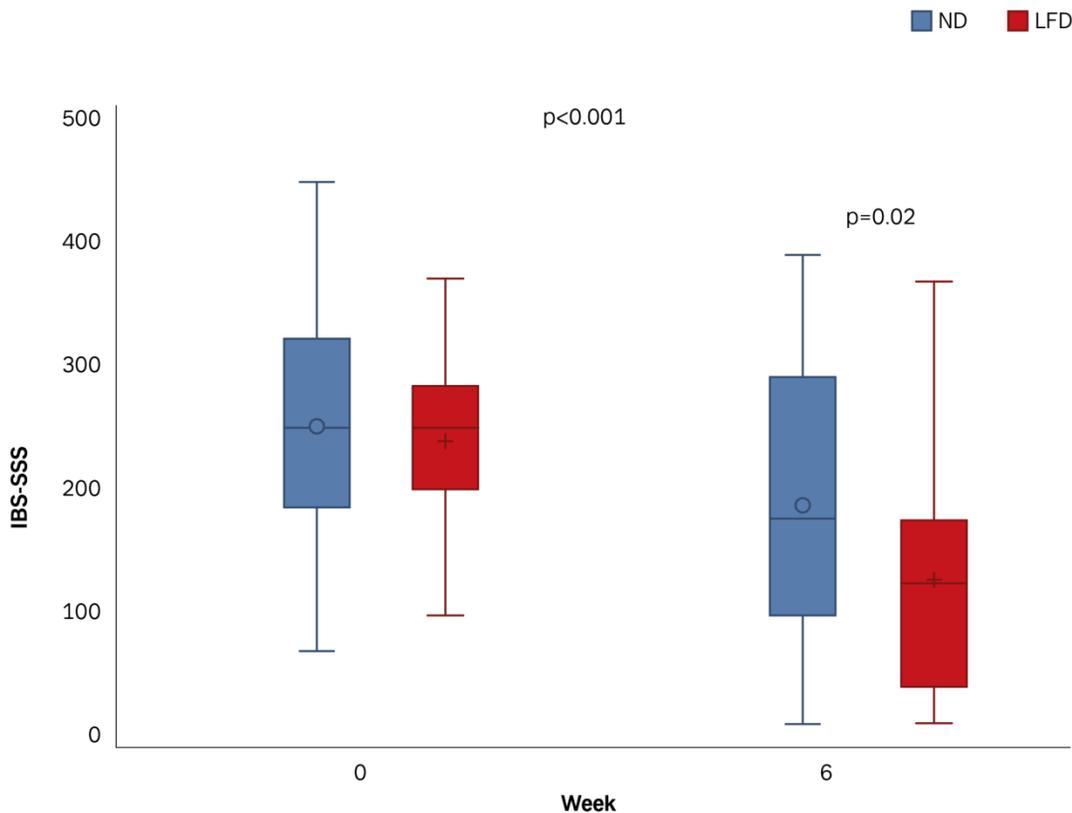

Figure 5. *Box of IBS-SSS crude data (means/quartiles/range) from the web-based program Constant-care for the ND and LFD groups for week 0 and week 6 in the intervention period. IBS-SSS: irritable bowel syndrome-symptom severity score; ND: normal Danish/Western diet; LFD: low FODMAP diet.*
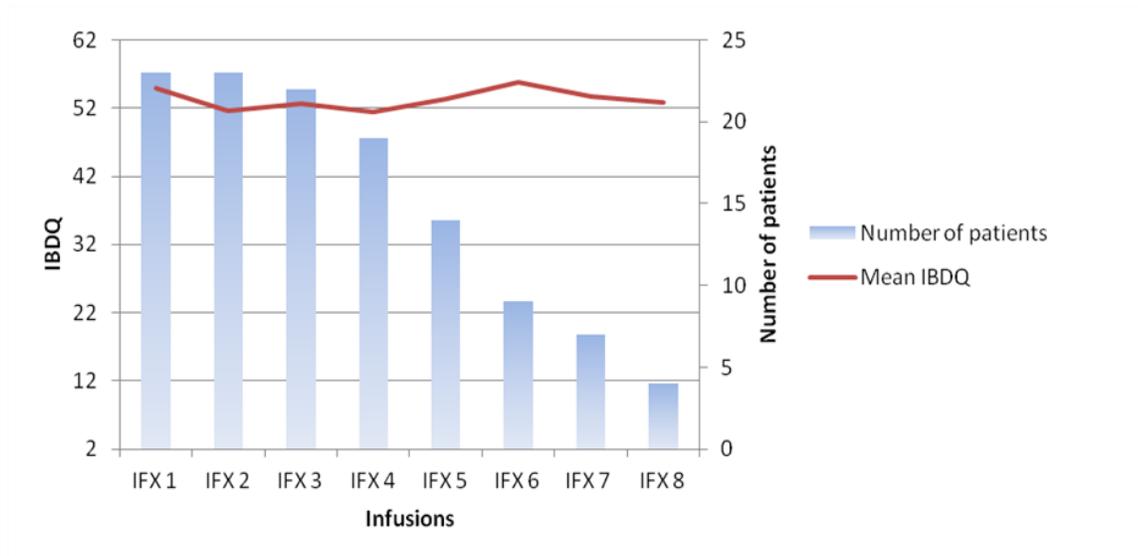
Figure 6. *Infliximab (IFX) infusions and quality of life according to the short-Inflammatory Bowel Disease Questionnaire (SIBDQ) on the day of infusion. X-axis: Ranking of infusions from first to eight from inclusion until end of the study. Y-axis: Scoring of quality of life (QOL) <50 poor; > 50 normal. Red line: Level of QOL on the day of the infusion*
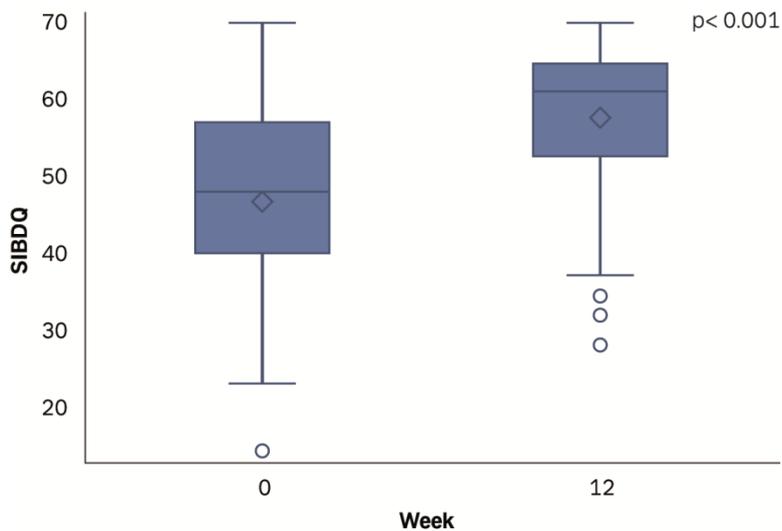

Figure 7. *Box plot of short inflammatory bowel disease questionnaire (SIBDQ) (means/quartiles/range) score changes from baseline to week 12 in patients with ulcerative colitis treated with mesalazine.*

Adherence to the web registrations in UC was even better, reaching up to 100% in total. The number of total weeks of follow-up of all patients during the study period was 904 weeks. The mean number of SCCAIs and FCs registered per patient during the study period was 13 and 12, respectively, as was required.

Adherence to mesalazine treatment was likewise improved. Adherence to former mesalazine treatment at baseline was a VAS median 88 (range 10-100) and a MARS median 23 (range 5-25), whereas adherence at the end of the study was a VAS median 100 (range 60-100) and a MARS median 24 (range 15-25) with a statistically significant improved adherence to mesalazine by VAS (p<0.001) and MARS (p<0.001).
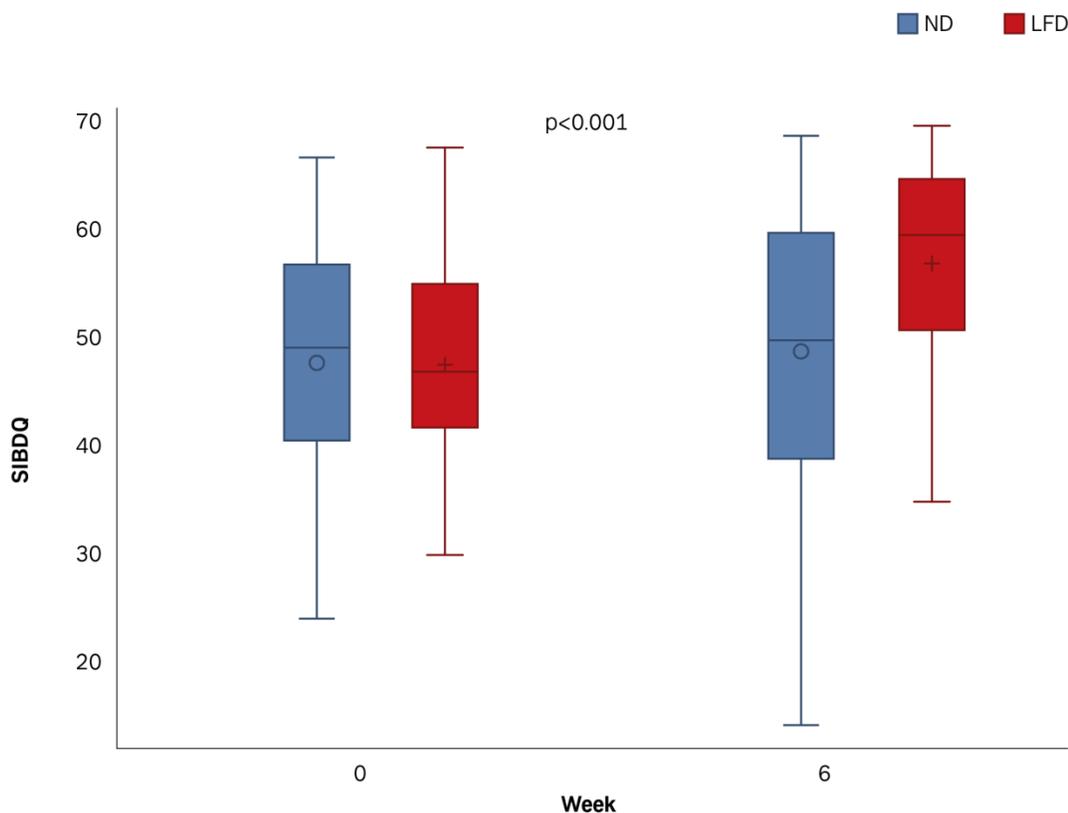
Figure 8. *Box plot of SIBDQ crude data (means/quartiles/range) for ND and LFD groups for week 0 and week 6. SIBDQ: short inflammatory bowel disease questionnaire; ND: normal Danish/Western diet; LFD: low FODMAP diet.*

In web-monitoring approach of IBS-like symptoms in patients with IBD, adherence to the diets (the quantity of FODMAPs in gram/day) was determined in all patients (100%) at week 0 and in 73 (94%) at week 6. At baseline, there was no significant difference in FODMAPs ingested by ND vs LFD patients, p=0.53. At the end of the study, the LFD patients had a significantly lower FODMAP intake, p<0.01, while those on a ND did not, p=0.35.

Table 5. *List of the adverse events (AEs) and severe adverse events (SAEs) in patients with CD on IFX and in patients with UC on mesalazine self-managed web-treatment.*

No.	Adverse event (AE)	Outcome
CD patients treated with Infliximab		
1	Urticaria	Resolved
2	Folliculitis	Hospitalisation
3	Severe relapse	Colectomy
4	Perianal abscess	Incision/Drainage
5	Perianal abscess	Incision/Drainage
UC patients treated with mesalazine		
1	Perianal abscess	Incision/Drainage
2	Headache	Mesalazine stop
3	Vertigo	Mesalazine dose reduction
4	Vertigo	Mesalazine dose reduction
5	Severe relapse	Hospitalisation

SAFETY AND SATISFACTION

Generally, the new web-based treatment applications were shown to be safe in various clinical situations, including for patients with various disease severities.

Regarding IFX web-treatment, significantly more adverse events (AEs) were registered in the control group than in the web group (45% vs 22%, p=0.002). However, there was no significant difference in hospitalisations (23% vs 22%, p=0.57), frequency of surgical interventions (7% vs 11%, p=0.39) or use of corticosteroids (9% vs 0%, p=0.34) when comparing web patients aFond controls.

In mesalazine web-treatment, 5 (6%) AEs were registered during the 12 weeks, of which only one was categorized as a severe AE (three days hospitalisation due to severe UC relapse shortly after allocation to mesalazine). Both CD and UC patients were satisfied with the web treatment (mean VAS score 9.0 and 8.2). The list of AEs in the web groups is presented in Table 5.

COSTS

The cost of IFX administered via web application was significantly lower than the cost of IFX administered via outpatient clinic (cost per patient per year: 11,502 EUR vs 12,062 EUR, p=0.001). In UC, the cost of mesalazine treatment administered via web was calculated to 3.22 (if 2.4 g/day mesalazine) and 6.32 (if 4.8 g/day mesalazine) USD per patient per day including database use, excluding FC analysis.

5. DISCUSSION

This thesis prospectively evaluates patterns of patients self-management using the new constant-care monitoring and treatment eHealth approaches, specifically designed in important clinical phenotypes to individualise the following treatments: i) IFX maintenance therapy in CD patients with moderate-to-severe disease activity, ii) Mesalazine in UC patients with active disease and iii) LFD in IBS patients and IBD patients with IBS. In this thesis, we describe the major outcomes of these approaches: disease outcome, quality of life, adherence, safety and costs.

THE NOVEL CONSTANT-CARE APPLICATIONS

Constant-care eHealth applications (61;86) are the first applications in IBD which include both an educational element and clinical monitoring (subjective as well as objective), and that provide patients with treatment advice. This makes the applications as close as possible to an outpatient clinic.

The basic principles of the constant-care applications presented in this thesis are the same as in the previous constant-care concept by Elkjaer et al (85). However, some new tools have been developed to empower patients with self-management: i) IB, consisting of subjective clinical scores and objective parameter (FC), to measure disease activity, ii) treatment guides for specific treatment regimens, iii) SMS notifications used to inform patients about the results of FC and reminding them to register their symptoms, and iv) export data function from the constant-care database to MS Excel allowing statistical analysis. Finally, patients were able to register additional questionnaires via the web applications to measure the adherence (MARS, VAS), satisfaction (SQ) and generic quality of life (SF-12) for the purposes of research.

To date, several eHealth-care systems have been developed to improve patients' access to health-care providers and disease outcome and to reduce costs.

The best-known leading international telemedicine systems for chronic diseases are the Veteran Health Administration (VHA), American Telemedicine Association (ATA) in USA (78;79) and the Whole Systems Demonstrator (WSD) remote care programme in the UK (74;75;110). These telemedicine technologies are designed to provide comprehensive support to chronic disease management (72;73;79;111), including IBD (83;112) and are based on in-home monitoring and treatment. The telehealth approaches, improving the patients' contribution to disease management, have different methodologies including specific guidebooks, telephone clinics, e-mail-correspondence, internet-based and specially developed self-management applications (77;113;114).

The web-based monitoring and treatment approaches in IBD (82;83;115-117) are more established in UC than in CD. The most well-known web-system in UC is the home automated telemanagement system (UC HAT) from the USA (112), consisting of an e-learning part and an IBD web-portal, allowing both patients and physicians to monitor symptoms (symptom diary), body weight, compliance with medication and any side effects of medication. Furthermore, visual and audio systems are included in the HAT (83).

Recently, the Southampton IBD virtual clinic (VC) in the UK linked to the gastroenterology outpatient clinic and integrated with the local laboratory and hospital administration systems have been implemented to replace traditional outpatient clinic for a selected group of patients (118). This clinic follow-up currently 20% of the Southampton IBD patients using the system and has proven to be efficient in managing stable IBD patients. It requires dedicated physician, IBD nurse specialist and IT support. In contrast, studies by Cross et al (82;83) on home telemanagement of the disease activity in patients with UC via a web-based clinical portal registry failed to show any significant benefit as regards the disease activity. However, this negative outcome might have been influenced by the lack of treatment advice in the web application.

The constant-care eHealth system was developed for disease management of chronic gastrointestinal diseases such as IBD (85;86) and IBS (119). Compared to the systems above it is a relatively new eHealth system, validated between 2006 and 2014 (86) for implementation in the current electronic patient record system.

Disease management in our applications is based not only on web-monitoring but also on web-treatment guide. This treatment guidance was for the first time introduced in the previous thesis by Elkjaer et al (86).

Recent meta-analysis has shown that self-management is feasible and changes the disease course for the better in the short-term (62). The same results were confirmed in a systematic review by Knowles et al (77). It has yet to be verified, however, whether web-guided management can impact the course of the disease in the long-term.

DISEASE OUTCOME BY WEB-TREATMENT IN CD AND UC

Using the web-treatment approach with IFX patients' inter- and intra-individual differences in need of IFX infusion were better reflected than by a conventional Q8 maintenance regime (16-18). Furthermore, with this individualised approach, the number of IFX infusions was reduced without worsening of the disease course. At the same time, the costs were reduced, and this is clinically important as such treatment requires considerable healthcare expenditure (120;121).

These results encourage IBD patients with the opportunity of maintenance treatment with biologicals at home, especially in subcutaneous administration (122-124). Nevertheless, this approach requires close collaboration between patient and IBD specialised health-care for supervision of the efficacy, immunogenicity and adverse events (125-127).

Using the web-treatment approach with MMX mesalazine in UC during 12 weeks, the treatment was individualised by optimising dosage and thus improving the disease course. In this study, 50% of UC patients with active disease on high dose (4.8 day) of MMX mesalazine achieved clinical remission at week 3 (21 day) and FC reduction (<100) at week 1 (7 days). Several trials have been shown efficacy of 4.8 g/day MMX mesalazine compared to 2.4 g/day for induction of remission in mild-to-moderate active UC (29;31;128;129). Likewise, a study by Osterman et al (130) demonstrates that MMX mesalazine dose escalation reduces relapse rates in patients with increased FC concentrations in quiescent UC.

Our results are similar to the previous constant-care web-guided treatment study developed by Elkjaer et al (61;86;131) and published in a Danish thesis, where UC patients with mild-to-moderate were randomized to self-managed web-guided treatment with any 5-ASA preparations versus standard care (usual outpatient clinic) for 12 months. The results of this study demonstrate the feasibility of the web approach, optimising disease outcome by reducing time to remission to 18 days in the web group versus 77 days in the control group.

Disease activity in this study was measured using clinical indices alone. In contrast, disease activity in our studies was measured by IB, which is a combination of clinical indices and FC, a validated non-invasive surrogate marker for endoscopic inflammation in IBD and a promising non-invasive tool for monitoring of the disease activity at home and as well in treatment with biologicals (90;98;130;132-134) as it is more sensitive surrogate marker for endoscopic disease activity and remission than clinical index (94-96). Moreover it can detect the inflammation at early stages (135;136).

However, other inflammatory markers such as leucocyte and platelet count, albumin, and lactoferrin may be required in monitoring of IBD using eHealth approaches (91;137;138). New rapid home tests for calprotectin at home to be implemented in self-management are developed by our group (131;139).

Patient education in self-management has a significant impact on disease outcome, as shown in a study by Robinson et al (64) in which, 15-30 minutes spent educating UC patients on how to self-manage their treatment, contributed to therapy self-initiation in 96% of the relapses. All patients in our studies had individual or group education in self-management during 1.5 hour. Several previous studies on self-management in IBD (62;64;84;140) showed that web-application treatment empowers patients with increased education, knowledge, and adherence, optimising disease control and reducing health care costs.

DISEASE OUTCOME BY WEB-MONITORING IN IBS
Self-management in IBS, until now, was available as Patient IBS Schools, self-help IBS guidebook and internet-based cognitive treatments (77;114;141;142). Our IBS constant-care approach was designed to monitor the IBS severity in patients with IBS and in IBD patients experiencing IBS-like symptoms. This approach is the first to use a web-based application to monitor IBS symptoms, IBS medication and quality of life. The application was designed for monitoring purposes only, without any treatment guides.
The web-based symptom monitoring approach in our study served as a kind of diary (119) in which the IBS symptoms and IBS-QOL were registered by patients on a weekly basis. This approach, in itself, may have an impact on IBS symptoms independent of dietary intervention.
Furthermore, educational elements such as information about the disease, the e-learning part (disease-specific and application-specific) and video clips to improve disease-specific knowledge had an impact on IBS.
Previous research has confirmed the positive impact of any intervention in IBS patients on symptom reduction (34;50;65;80;81;114;143-145). Likewise several self-management concepts developed in the IBS field have been demonstrated a psychological and therapeutic impact (37), considerably improving IBS symptoms and quality of life in a study by Hunt et al (146). However, in our study a LFD by itself was observed to significantly ameliorate IBS symptoms when compared to the control group, which also used the web-monitoring programme. This suggests that LFD may be efficacious in IBD patients suffering from IBS. Several previous studies have substantiated the efficacy of LFD in patients with IBS in Australia, New Zealand, the UK, as well as in Denmark (54;55;57-59;147-149). However, the effect of LFD on IBS-like symptoms in IBD patients has, to date, been studied in only one retrospective, non-controlled study by Gearry et al (60) in Australia. In this study, 72 IBD patients who received dietary advice at least 3 months beforehand underwent a telephone questionnaire examination on IBS-like symptoms. The authors found significantly reduced abdominal pain, bloating and stool consistency (diarrhoea) in these patients on a LFD.
Thus these applications have a positive impact not only on monitoring, but also on treatment effect and are cost-effective in patients with IBS (141).

Quality of life
Quality of life among patients is one of the most important parameters for evaluating the overall quality of treatment care. Quality of life improved significantly in our patients using web-treatment and monitoring approaches, similarly to previous concept (85). These results are consistent with the results from other studies showing an improvement in quality of life using eHealth approaches (83;85;119;150). However, a recent study by Cartwright et al (151) revealed that telemedicine had no influence on quality of life and psychological outcomes in patients with diabetes, COPD, or heart failure.
Though a decrease in disease activity is a significant factor influencing quality of life, there are several other factors which play an important role. These include education and improved disease-specific knowledge, easy access to care providers from home, and the possibility of early treatment in case of disease worsening (61;83).

Adherence
Adherence to the web-treatment and monitoring approaches was high in our studies, as in the previous study, and contributed considerably to optimising the course of the disease (85). The likely reason for good adherence in our studies was patient education prior to the studies and easy access to care providers via these web applications (79;116). Furthermore, low pill burden (preferably once daily) and avoidance of multiple therapies in our UC study with MMX mesalazine treatment was other factor influencing the adherence (152-154).
Our results are consistent with the study by Elkjaer et al (61) demonstrating that adherence to 4-week acute treatment with 5-ASA preparations increased with 31% in web patients as compared to the control group. Low-rates of non-adherence (5-30%) have been shown in clinical trials due to intensive supervision of patients by study nurse and doctors (24), while high rates of non-adherence is present in clinical practice to long-term medications (25). Non-adherence to therapies has been shown to have a negative impact on disease outcome, increasing the risk of relapse in UC more than five-fold in patients not taking 5-ASA treatment (23).

Adherence to the LFD in IBD patients was high and the good results seen here were influenced by close collaboration with nutritionists. In primary care, physician-patient concordance was shown to significantly improve compliance (155). Treatment reminders and SMS notifications integrated in our program guides also contribute to the treatment adherence in addition to the e-Learning program.

Satisfaction and safety
Overall, patients in our studies were satisfied with the web-based approaches. Prior eHealth studies showed similar results (61;112;117). However, a study by Young et al (156) suggested that patients were dissatisfied with the eHealth approach due to difficulty accessing the care coordinator and their subsequent slow response; this was in contrast to our studies.

The new constant-care approaches have been deemed safe as no signs of increased occurrence of AEs were observed with regards to web-treatment. In our CD study the number of hospitalisations and surgery were similar to standard-care. Likewise, in the UC study no increased rates of hospitalisations and/or surgery during study period was observed.

The programs were secure in respect of patient privacy and data protection. Each user had administered a secure username and password for accessing the program. The patient had access to the registration, results, treatment guide and educational parts of the application, as well as to a contact person. The health-care provider had access to the results, missing registrations, treatment status and to contact patients to adjust the treatment and to monitor complications.

Costs
The novel constant-care approaches presented here, as with other studies, were shown to be cost-effective when compared to standard care costs (64;73;85;116;140;141;157). Moreover, the costs of these approaches were influenced by careful monitoring of disease activity based on weekly FC analysis and symptom registration and required involvement of care providers due to the nature of the research. Thus, web-monitoring in daily clinical practice would be less frequent and the costs would accordingly be reduced.

Similarly, in heart failure (76;158) and in the other chronic conditions, evaluation of home telehealth showed reduced hospitalisations and increased cost-effectiveness (159).

In contrast, the costs of some telehealth rehabilitation approaches in older patients have been either similar to standard care (159) or higher than in standard care (110). A recent systematic review of eight studies by Kumar et al (160) reports that the costs of telemedicine applications are substantial and must be carefully considered when initiating, evaluating and implementing such applications.

Finally, telemedicine communication solutions can help chronic patients with reducing those costs not only directly associated with their medical care, but also with indirect costs incurred from transport, loss of working hours etc., which may contribute to both private and public savings (161). Hence, these savings could be applied to patients with severe disease, requiring hospitalisation and surgery.

STRENGTH AND LIMITATIONS OF THE NOVEL CONSTANT-CARE APPLICATIONS
The strengths of the novel constant-care applications are that these were tailor-made solutions and were shown to be feasible and effective not only for IBD patients in remission or with mild-to-moderate disease activity, but also for patients with moderate-to-severe CD and treatment with biologicals, as well as for relapsed UC patients on MMX mesalazine. Furthermore, the implementation of the IBS web-monitoring application is the first eHealth web-based approach of its kind. For the first time, IB for home monitoring of disease activity was introduced in our web-applications and might be a pragmatic tool in other telemedicine concepts generally.

The main limitation of the new constant-care web-based approaches is the lack of a randomised controlled design with a prospective standard-care control group and lack of blinding of the treatment. However, this comparison was provided by Elkjaer

et al (85). Blinding the web-intervention would not be possible, as patients need to be informed about treatment conditions.
A further limitation is the use of telemedicine in severely ill patients requiring rapid face-to-face consultation, acute hospitalisation and rescue therapy. Our programs are instead best used in CD and IFX treatment and in UC with mesalazine, as the programs guide the patient to increase the dose and contact their doctor immediately in a case of severe relapse or alarm symptoms.

The challenges of telemedicine consultations derive from the communications being based on electronic registrations, writing digital communication and telephone/video communication between patients and health-care providers. In this kind of communication the physician may lack the history of the disease, physical examination and investigation needed for diagnosis (162). Moreover, telecommunication depends on accessibility to the care coordinator, of technical equipment functionality and patient willingness to self-manage (156). In a RCT trial a self-report questionnaire about physician-patient communication revealed that patient communication during telemedicine was not inferior to physician communication (163). In our studies, patients had direct contact with a physician and IBD nurse via an email generated from constant-care and through telephone contact. There were no registered difficulties with the use of the web-approaches or telecommunication equipment.

The limitations of the present studies are the sample size in both CD and UC studies, (study I, II) both of which are small and include no group comparison for the main clinical outcome measures. In the IBD and IBS studies (study III, IV) and treatment with LFD, one of the major limitations is the lack of a blinded diet. To blind the diet in such studies is difficult but possible, as in the study by Halmos et al (59). However, this design requires special kitchen facilities for delivery of blinded food and is very expensive to carry out.
Furthermore, our studies are of short-term and the patients were quite heterogeneous regarding diagnosis and disease activity upon entry into the study (study IV). Endoscopic control of the patients participating in these trials should have been performed at the beginning and at the end of these studies to control for the effectiveness of the treatment

6. CONCLUSIONS AND PERSPECTIVES
In this thesis, we have further substantiated the value of the constant-care web-monitoring and treatment concept as a powerful tool in optimising the treatment and the disease course in CD patients on IFX, in UC patients on mesalazine, and in the monitoring of IBS.
These eHealth strategies represent a novel approach in patient self-management of disease monitoring and treatment decisions. Self-management strategies provide the patient with opportunities to easy and quick access to medical care, provide more individualised treatment and represent a unique opportunity for a select group of patients with IBD that require life-long follow-up and treatment. By integrating self-monitoring and/or self-treatment in IBD care, it is anticipated that the length and burden of inflammation, as well as the time to remission, can be improved. New technologies and digital solutions continue to impact on IBD healthcare, with telemedicine being increasingly used for follow-up and treatment especially young, busy or rural IBD and IBS patients with limited time or reduced access to standard care providers.

Web-based approaches are relatively new in this field and offer a promising, cost-reducing tool for of follow-up and treatment as an alternative to traditional outpatient settings.

Based on the evidence to date, eHealth technology is a tool that could potentially also enhance long-term prognosis of gastrointestinal diseases. However, the long-term influence of eHealth on mortality, cancer and surgery rates has yet to be documented.

In Denmark, there are not currently any active telemedicine solutions in use. Hopefully, concepts such as constant-care are to be implemented in the coming years in the Danish health system. Recently, a large trial using the eHealth clinically integrated home monitoring platform (KIH) among patients with diabetes, COPD and IBD, as well as pregnant women, was carried out and is in the evaluation stage, with plans to implement the system in daily clinical care during 2015. The constant-care system is a core aspect of the IBD part of this platform (www.egastro.constant-care.dk) and is also planned to be implemented in Sealand and the Capital Region of Denmark during 2015-2016. Along with this, the constant-care concept is under continuous development. Currently, two new constant-care web applications focusing on specific patient groups are in development: www.grav.constant-care.dk for the web monitoring of the disease course of IBD patients who are pregnant and www.young.constant-care.dk for the web monitoring and treatment of children and adolescents with IBD. Furthermore, new clinical tools such as a home faecal calprotectin test (CalproSmart) and blood test (AnemiaSmart) are in development to be used by patients at home; these will enable patients to receive immediate results, as opposed to the delay (approx.14 days) associated with traditional laboratory testing using the ELISA method. Overall, the present thesis is to be seen as a step on this path towards implementation of eHealth care in patients with gastrointestinal diseases in Denmark.

7. SUMMARY

Background: Inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS) are chronic gastrointestinal disorders of unknown etiology of increasing incidence and changing disease activity or severity. Approximately 60-80% of IBD patients suffer from IBS. Monitoring and treatment goals of IBD are to optimise the disease course by prolonging remission periods and preventing or shortening periods of active disease. Constant-care web-monitoring and treatment approaches with active patient involvement have been proven effective in UC, increasing patients' adherence and improving the disease outcomes.

Aim: To assess the feasibility and efficacy of the novel constant-care eHealth applications in i) CD patients treated with infliximab (IFX), ii) UC patients with active disease on mesalazine, iii) IBS patients and iv) IBD patients with IBS on a low FODMAP diet (LFD).

Methods: New constant-care web applications www.cd.constant-care.dk, www.meza.constant-care.dk and www.ibs.constant-care.dk in IBD patients were developed and assessed in this thesis. An integrated inflammatory burden measure of disease activity, consisting of a subjective (clinical indices) and of an objective (faecal calprotectin) part and a treatment guide to drug doses and intervals, was incorporated into the web applications and used by patients.

Results: Web-guided IFX treatment in CD demonstrated patients' inter- and intra-individual variability in infusion intervals and provided patients with individualised treatment according to their
needs. Web-guided treatment with multimatrix mesalazine was efficacious in a majority of UC patients with mild-to-moderate disease activity. Web-guided IBS-monitoring in IBD and in IBS patients on LFD was shown to be a feasible method that actively involved patients in their disease management and had a positive short-term impact on the disease. Moreover, the new constant-care concepts were demonstrated to be safe and to have a positive impact on quality of life and adherence to treatment and helped to reduce the costs.

Conclusions: The novel constant-care web applications have proven feasible in improving the disease outcomes in CD patients on IFX, in UC patients on mesalazine, and in monitoring IBS. These applications are expected to be implemented in the clinical practice of gastroenterology in Denmark in the coming years. Future studies will help to assess whether the natural disease course can be improved in the long-term.

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