The PROMise of remote monitoring to improve quality of care for inflammatory bowel disease

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Marin de Jong

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The PROMise of remote monitoring to improve quality of care for inflammatory bowel disease

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Marin Joanne de Jong
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Promotor

Prof. dr. A.A.M. Masclee

Co-promotores

Dr. M.J. Pierik

Dr. A.M. van Tubergen

Beoordelingscommissie

Prof. dr. M.P. Zeegers (voorzitter)

Prof. dr. S. Vermeire (Katholieke Universiteit Leuven)

Prof. dr. D.W. Hommes (Leids Universitair Medisch Centrum)

Prof. dr. H. P. Brunner-La Rocca

Dr. H.J.M.M. Mertens

CONTENTS

Chapter 1	General introduction and outline of this thesis	9
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Part I

Chapter 2	Patient-reported outcome measures for use in clinical trials and practice in inflammatory bowel diseases – a systematic review	27
Chapter 3	Development and validation of a patient-reported score to screen for mucosal inflammation in inflammatory bowel disease	53

Part II

Chapter 4	Development and feasibility study of a telemedicine tool for all patients with IBD: MyIBDcoach	75
Chapter 5	Telemedicine for management of inflammatory bowel disease (myIBDcoach): a pragmatic, multicentre, randomised controlled trial Building evidence for care beyond the medical centre – editorial commentary	95
Chapter 6	Telemedicine directed specialised care for inflammatory bowel disease is cost-effective. A cost-utility analysis of the myIBDcoach trial	133

Part III

Chapter 7	Novel perceived stress and life events precede flares of inflammatory bowel disease: a prospective 12-month follow-up study	151
Chapter 8	The risk of an impaired nutritional status precedes flares in IBD outpatients	167
Chapter 9	Exploring conditions for redistribution of anti-TNFs to reduce spillage. A study on the quality of anti-TNF home storage	181
Chapter 10	The prevalence of latent tuberculosis and hepatitis B after systematic screening of patients prescribed biological therapy in a low-endemic area	193

Chapter 11	General discussion	199
Epilogue	Summary	217
	Samenvatting	223
	Valorisation	231
	Publications, presentations and awards	241
	Dankwoord	248
	Curriculum Vitae	255

Chapter 1

General introduction

Inflammatory bowel disease

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract characterised by periods of exacerbation and remission. Evidence shows that a complex interaction between intestinal microbiota, environmental factors and an altered immune response in genetically susceptible hosts causes IBD¹. As a result of the complex aetiology, the clinical presentation of the diseases is very heterogeneous, as shown by variations in disease location and behaviour, relapse frequency, the occurrence of extra-intestinal manifestations, complications, and response to treatment among individuals (figure 1 and 2)^{2, 3}. Worldwide, the incidence of IBD is increasing with highest rates reported in Western countries (up to 29.3/100,000 in CD, and 24.3/100,000 in UC), resulting in more than 2.5 million people suffering from IBD in the European continent^{4, 5}. As IBD affects young people in the most productive years of their lives⁽⁶⁾ and requires life-long monitoring and therapy, the disease has a significant impact on patients' quality of life and constitutes an economic burden due to direct and indirect healthcare costs^(7, 8). IBD is also associated with an increased prevalence of psychological morbidity⁹.

Figure 1. A) Phenotype of Crohn's disease following the Montreal classification; disease extent (L) and behaviour (B). B) Major extra intestinal manifestations and associated autoimmune disorders. Figure adapted from Baumgart et al. *Lancet* 2012; 380: 1590–1605.

The current treatment target for IBD is to achieve and maintain steroid-free clinical remission and to prevent structural bowel damage, such as fistulas, abscesses, intestinal strictures, and surgery. To achieve these targets, different therapeutic strategies are

applied. The traditional treatment strategy is a step-up approach, in which therapy is started with the least potent and least toxic medication followed in sequence by escalation to more powerful agents with potentially more side-effects, if remission could not be achieved with therapy from the previous step¹⁰. Since the long-term outcome with this strategy was often unfavourable, a top-down strategy, especially for patients presenting with severe disease, was introduced for quick establishment of endoscopic remission (figure 3)¹⁰⁻¹⁶. As a result, there has been an increase in the number of patients exposed to immunosuppressive agents and biological therapy earlier in their disease course. As these drugs can have serious side effects, such as severe infections, accurate monitoring of medication use and side effects in IBD patients is warranted.

Figure 2. Phenotype of ulcerative colitis following the Montreal classification. Symptoms and treatment strategy can differ based on extent of disease. Figure adapted from Ungaro et al. *Lancet* 2017; 389: 1756–70.

Figure 3. Treatment pyramid for inflammatory bowel disease. AZA, azathioprine; 6-MP, 6-mercaptopurine; MTX, methotrexate

Monitoring disease course and management strategies for IBD

The most important long-term outcomes for IBD used in clinical trials are the number of flares, corticosteroid use, hospitalisations, complications (i.e. fistulas, abscesses and strictures) and surgery. Population based cohorts showed that the numbers of surgeries and hospitalisations decreased in parallel with more frequent and earlier prescription of immunosuppressives and biologicals¹⁷⁻¹⁹. However, despite high exposure of new and costly biological therapies, the risk of disease progression from an inflammatory to a stricturing or penetrating phenotype has not changed over the past decades¹⁷. Therefore, new management strategies are proposed to improve long-term disease outcome¹¹.

Several studies showed that in patients with rheumatoid arthritis, serial monitoring with objective scoring tools and early treatment adjustment was found to result in lower disease activity and better long-term outcome^{20, 21}. In IBD, mounting evidence underlines the importance of tight control of disease activity and early intervention in case of recurrence of intestinal inflammation to prevent irreversible bowel damage^{11, 22-25}. In this context, the treatment target changed from clinical remission alone, to deep remission (endoscopic remission or even histologic remission)²⁶. In addition, monitoring factors affecting disease activity, such as non-adherence to treatment, unfavourable nutritional status, smoking, and psychological factors have shown to improve disease outcome²⁷⁻²⁹. Targeted interventions on these aspects can contribute to a reduction of disease relapses, healthcare utilisation including hospitalisation and absence from work in subsets of patients²⁷⁻²⁹.

Objective measures of mucosal inflammation are important for implementation of a tight control strategy. In IBD, the gold standard for assessment of disease activity is endoscopy. This examination is however invasive, costly and time-consuming and therefore not suitable nor available for frequent evaluation. Non-invasive biomarkers such as C-reactive protein (CRP) and fecal calprotectin (FC) are among the best studied markers of inflammation in IBD. Multiple studies found that these markers predict a relapse of IBD with sensitivity and specificity values ranging from 50-90%, with the highest values for FC and depending on cut-off values and clinical setting¹¹. In addition, clinician-reported clinical activity indices as the Harvey Bradshaw Index (HBI), Crohn's Disease Activity Index (CDAI), or Simple Clinical Colitis Activity Index (SCCAI) are frequently used for monitoring of disease activity over time. However, these clinical indices only moderately correlate with endoscopy and have shown to poorly predict endoscopic remission³⁰.

As an alternative, patient-reported outcome measures (PROMs) are increasingly of interest as incorporation of health outcomes that reflect patients' perspectives on healthcare is advocated to support patient-centered care and to improve value of healthcare^{31, 32}. Systematic registration of these PROMs, and patient-reported experiences measures (PREMs) is increasingly requested by healthcare insurers and governments to

measure quality of care, benchmark and guarantee reimbursement of expensive drugs or treatments. At the same time, patients themselves also demand empowerment and more involvement with their therapy. Different PROMs have been developed for follow-up of disease activity, such as the Manitoba IBD Index³³, the single-item numeric rating scale³⁴, the IBD-10³⁵ and questionnaires derived from the Harvey Bradshaw Index³⁶⁻³⁸, the Simple Clinical Colitis Activity Index³⁷⁻⁴¹, the Crohn's Disease Activity Index^{42, 43} and the Mayo Clinic Score⁴⁴⁻⁴⁶. However, their value in predicting mucosal inflammation is unknown as none of these have been validated relative to endoscopy.

Current IBD healthcare organisation

IBD is diagnosed through a combination of endoscopic, radiologic and laboratory tests⁴⁷. After diagnosis and induction of remission, IBD care is traditionally organised by routinely scheduled follow-up visits and laboratory controls with a frequency based on medical treatment, but independent of the occurrence of unpredictable flares (figure 4). In the Netherlands, patients visit the outpatient clinic on average 3 times per year. In case of a flare, patients visit the outpatient clinic 2-3 times extra depending on the severity. For severe flares or complications, patients might be hospitalised or require surgery.

Due to a rising incidence of IBD over the past decades and a shortage of gastroenterologists in the Netherlands, outpatient clinics tend to be overburdened. As a result, implementation of tight control strategies and monitoring and intervening on factors affecting disease activity is impossible in the current healthcare organisation. In addition, analysis of the population based IBD hospitalised South Limburg cohort showed that direct healthcare costs continue to increase over time (figure 5). However, there is no data confirming whether these increased costs are accompanied by an increase in quality of life, reduction of (work)disability or improved disease outcomes. Therefore, insurance companies, governments and patient organisations increasingly demand registration of doctor-reported and patient-reported quality parameters. This has, however, not yet been systematically implemented in current clinical practice, because acquiring all the necessary information at the right moment for every individual patient remains a challenge. For these reasons, structural healthcare reorganisation is warranted.

Figure 4. Organisation of IBD care. After the diagnosis of IBD, patients are classically followed at the outpatient clinic with visits and laboratory tests. An induction therapy is started and evaluated with endoscopy/ radiology or laboratory tests. When a patient achieves remission of the disease, follow-up consists of outpatient visits and phone consultations for monitoring of remission and medication side-effects. In case of a relapse, the cycle restarts. When a patients presents with acute severe disease or treatment refractory disease, hospitalisation and/or surgery might be needed.

Figure 5. Mean direct healthcare costs for CD patients per year after diagnosis over three different era's; era '91-98, era '99-05 and era '06-11. *Lalisang et al. The direct healthcare costs of Crohn's disease increased over the last two decades in a Dutch population-based cohort presented at ECCO 2018.*

Telemedicine

As smartphone adoption is increasing rapidly worldwide, telemedicine is gaining ground. Telemedicine, literally defined as healthcare at distance, allows healthcare professionals to evaluate, diagnose and treat patients in remote locations using information and communication technologies (ICT). Many telemedicine tools are available, most of which provide health information or support data collection. However, over the past decade, telemedicine tools for chronic diseases attract attention as they assist in monitoring of symptoms or objective measurements as blood pressure or weight. Additionally, these tools aid healthcare professionals to implement a tight control strategy by monitoring patients at home between outpatient visits. They allow for strict and instantaneous follow-up of symptoms and intestinal inflammation, and facilitate timely, and personalised interventions. At the same time, these tools can automatically monitor factors influencing disease as medication (side-)effects, medication adherence, nutritional status, smoking, and psychological factors.

In other chronic relapsing-remitting diseases, such as chronic obstructive pulmonary disease and heart failure, telemedicine has shown to improve quality of care and to reduce the use of healthcare resources and related costs^{48,49}. Also for IBD patients, data on several telemedicine systems was available at start of this project. Cross *et al.* developed a Home Telemanagement System for UC patients⁵⁰⁻⁵⁵, composed of a netbook computer and an electronic weight scale that monitors symptoms, medication use and

side-effects. Elkjaer *et al.* developed a web-based system (Constant Care) to monitor disease activity and quality of life in patients with mild-to-moderate UC on 5-aminosalicylic acid (5-ASA) treatment^{56, 57}. This program was also used for individualisation of 5-ASA treatment and improvement of adherence in mild-to-moderate UC patients²⁷ and for individualisation of infliximab (IFX) scheduling in CD patients on IFX maintenance treatment⁵⁸. Overall, these systems were shown to be feasible, safe and well-accepted by IBD patients. However, they were developed for patients with specific subtypes of IBD with relatively mild disease and studies provide inconsistent results on the effects of these telemedicine systems on disease outcome^{53, 56, 59}. This together compromises their use in real-world settings^{17, 36-38, 60}. In addition, lack of a conceptual framework for the development, evaluation, and implementation of telemedicine systems⁵⁹, a disconnect between users and developers of health IT systems⁶¹, and financial hurdles such as reimbursement of telemedicine consultations by insurance companies, contributed to a lack of implementation in daily care.

Aim of this thesis

This thesis describes the development and implementation of a telemedicine tool for all IBD patients in order to reorganise IBD care towards efficient, personalised and higher value care.

Part I of this thesis focuses on patient-reported disease activity measures. **Chapter 1** reviews the available PROMs for assessment of IBD disease activity and their diagnostic accuracy. **Chapter 2** describes the development and validation of a new patient-reported disease activity score relative to the golden standard endoscopy.

Part II of this thesis focuses on the role of telemedicine for management of IBD. **Chapter 3** describes the development and pilot-testing of myIBDcoach, the first telemedicine system that monitors and registers disease activity in patients with all subtypes of IBD. To investigate the effects of use of myIBDcoach compared to standard care on healthcare utilisation and patient-reported quality of care, a pragmatic randomised multicentre trial was carried out of which the results are presented in **chapter 4**. Subsequently, cost-effectiveness of use of myIBDcoach is described in **chapter 5**.

Part III of this thesis covers the opportunities of telemedicine to collect data on factors believed to influence disease activity, such as psychological factors (**chapter 6**), nutrition (**chapter 7**), medication adherence and storage (**chapter 8**) and medication side-effects, such as severe infections (**chapter 9**).

The epilogue contains a general discussion of the results described in this thesis and provides opportunities and suggestions for further research.

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PART I

Chapter 2

Patient-Reported Outcome Measures for Use in Clinical Trials and Clinical Practice in Inflammatory Bowel Diseases: A Systematic Review

Marin de Jong, Roxanne Huibregtse, Ad Masclee, Daisy Jonkers
and Marieke Pierik

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ABSTRACT

Background: Mucosal inflammation must be carefully monitored to improve the long-term outcomes of patients with inflammatory bowel diseases (IBD). Patient-reported outcome measures (PROMs) are used increasingly to monitor disease activity in clinical practice and as endpoints in clinical trials. We performed a systematic review to provide an overview of the available PROMs on IBD activity and to evaluate their diagnostic value.

Methods: A systematic search of the PubMed, Medline, Cochrane library, and Embase databases using defined keywords, identified 973 articles. These were screened by 2 independent reviewers, and 37 articles on development or validation of PROMs to assess IBD activity were identified for further analysis. Based on the recommendations of the Food and Drug Administration (FDA), the following measurement properties were evaluated: content, construct, and criterion validity; reliability; and responsiveness to change. In addition, data on ease of use in clinical practice were collected.

Results: Seventeen articles presenting 20 different PROMs were included in the final analysis, although none met all the FDA-recommended criteria. Only 2 PROMs (patient-reported Harvey Bradshaw Index and Simple Clinical Colitis Activity Index scores) reported patient involvement during its development. Only 6 PROMs (patient-reported global assessment, patient assessment of disease activity, mobile health index for Crohn's disease, mobile health index for ulcerative colitis, patient-reported outcome derived from the Mayo score, and the 6-point Mayo score) were validated as markers of IBD activity, using findings from endoscopy as the reference standard; these PROMs identified patients with mucosal inflammation with area under the curve values of 0.63–0.82. The mobile health index for CD and UC scores had the best measurement properties for use in clinical practice and in clinical trials.

Conclusion: In a systematic review, we identified more than 20 PROMs that have been developed and tested for their ability to determine IBD activity. Further studies are needed to determine their accuracy and whether they can be used effectively in routine practice, clinical trials, telemedicine systems, and value-based healthcare programs.

INTRODUCTION

Inflammatory bowel diseases (IBD), including the two main subtypes Crohn's disease (CD) and ulcerative colitis (UC), are characterised by a heterogeneous clinical manifestation and a chronic relapsing-remitting course¹. Two important novel insights prompt the use of patient-reported outcome measures (PROMs) for optimal management of IBD patients. First, to prevent disease progression and improve the long-term disease outcome, including complications, hospitalisation and surgery, management of IBD is shifting from mere control of symptoms towards tight control of mucosal inflammation and early intervention in case of a relapse². Mucosal inflammation, further referred to as disease activity, is ideally assessed by endoscopy; however, this examination is too invasive and costly for frequent evaluation. Therefore, non-invasive biomarkers such as C-reactive protein (CRP) and fecal calprotectin (FC) or clinician-reported activity indices as the Harvey Bradshaw Index (HBI), Crohn's Disease Activity Index (CDAI), or Simple Clinical Colitis Activity Index (SCCAI) are frequently used for monitoring of disease activity over time. As an alternative, PROMs, for instance incorporated in telemedicine systems, could assist healthcare professionals to implement a tight control strategy in a setting of an increasing IBD incidence with limited healthcare resources^{3,4}. Secondly, the focus of healthcare is transitioning from volume-based towards value-based systems, in which patient outcomes are evaluated relative to cost of care^{5,6}. Insurance companies, governments, and patient organisations demand registration of PROMs as efficacy endpoints of interventions in routine care. In addition, the use of patients' perspectives on the effectiveness of therapies in clinical trials is strongly recommended by the Food and Drug Administration (FDA)^{5,7,8}.

The definition of a PROM is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else and without laboratory assessments⁸. The FDA has provided guidelines on how a PROM should be developed⁸. First, item generation of a PROM should be established by focus groups interviews containing a heterogeneous group of patients regarding population characteristics, condition and treatment. Thereafter, its construct validity, criterion validity, reliability and ability to detect change should be evaluated to finalize the instrument^{7,8}.

For IBD it is important to distinguish PROMs monitoring disease activity, from PROMs evaluating patients' perspectives on for example disease control and quality of life. Systematic evaluation of both is important to improve the long-term outcome and value of care for IBD patients. A wide variety of PROMs for monitoring of disease activity in IBD patients has been developed over the past two decades. The aim of this review was to provide an overview on these PROMs and to evaluate their measurement properties.

MATERIALS AND METHODS

Search strategy for identification of studies

A structured literature search up to December 2016 was conducted using Pubmed, Medline, Embase and the Cochrane Library to identify all articles on the development or validation of PROMs measuring disease activity in IBD patients. Both MeSH subject headings and truncated text-words including “Inflammatory bowel disease”, “Crohn’s disease”, “ulcerative colitis”, “disease activity”, “score”, “questionnaire”, “index”, “measurement”, “patient-reported outcome measure”, “self-reported”, and similar keywords were used.

Criteria for study selection

Two authors (MJdJ, RH) independently reviewed titles and abstracts from the search strategies and identified eligible studies. Full texts were obtained and reviewed when articles met all of following criteria: 1) English language, 2) published in an international peer-reviewed journal, 3) assessing adult or pediatric IBD patients (UC, CD or both), 4) reported on patient-reported questionnaires measuring disease activity, 5) contained data regarding diagnostic accuracy of the questionnaire compared to endoscopy, or to laboratory parameters such as CRP, FC or Erythrocyte Sedimentation Rate (ESR), or to clinician-reported disease activity questionnaires, such as the physician global assessment (PGA), Crohn’s Disease Activity Index (CDAI), Harvey Bradshaw Index (HBI), Simple Clinical Colitis Activity Index (SCCAI), Pediatric Ulcerative Colitis Activity Index (PUCAI), or Mayo score (full Mayo score: stool frequency, rectal bleeding, endoscopic examination and PGA (12-item), partial Mayo score: stool frequency, rectal bleeding and PGA (9-item)). A third reviewer was consulted to reach consensus in case of disagreement.

Data collection

Two reviewers carried out the data extraction using a standardised data extraction form and discussed the content in case of disagreement. Characteristics of the PROMs noted included: study population, language, items being measured, administration mode (paper or digital), recall-period, scoring and cut-off values. The FDA has provided guidelines on how a PROM should be developed and which measurement properties should be evaluated⁸. First, content validity which is defined as the extent to which an instrument measures the concept of interest. Second, construct validity which is determined by evidence that a relationship exists with another accepted measure of disease activity. Third, criterion validity which represents the extent to which a PROM is related to a generally accepted gold standard measure, which is endoscopy for IBD disease activity. In addition, when a PROM is developed for measurements over time, for example in clinical practice or clinical trials, its adequacy also depends on its reliability to yield consistent scores over time when no change is expected in disease activity. At last, the ability of a

PROM to detect differences in scores over time (responsiveness) in individuals who have changes in disease activity is important⁸. The abovementioned measurement properties were extracted from the included articles.

The following interpretations of statistical measures used to compare (clinical, endoscopic or biochemical) disease activity scores were applied: correlational measures (ρ) were interpreted as 0.10-0.29 no/negligible correlation, 0.30-0.49 low correlation, 0.50-0.69 moderate correlation, 0.70-0.89 high correlation and 0.90-1.00 very strong correlation. For Cohen's kappa (κ) measure of agreement the following definitions were used: <0.4 poor, 0.4-0.6 fair/moderate, 0.6-0.8 substantial/good and 0.8-1.0 excellent. Area under the curve (AUC) values were considered as 0.5-0.7 representing poor, 0.7-0.9 moderate and >0.9 high accuracy. A sensitivity of $\geq 80\%$ and a specificity of $\geq 80\%$ were considered positive indicators of the respective measurement property.

RESULTS

Study selection

The search strategy resulted in a total of 973 hits. Details on the selection process can be found in the flow chart (figure 1). After removing duplicates and screening articles by title and abstract, 37 studies remained for full text assessment. Twenty articles were excluded for the following reasons: the reported instrument was not patient-reported¹⁰; the reported instrument did not assess disease activity⁶; the article did not provide measurement properties of the PROM⁴. Finally, 17 articles were included covering the following instruments: self-administered SCCAI⁹, 6-point Mayo score^{10, 11}, patient-assessment of disease activity¹¹, Manitoba inflammatory bowel disease index (MIBDI)¹², survey-index CDAI (S-CDAI)¹³, patient-based PUCAI¹⁴, patients' global assessment¹⁵, patient-SCCAI (p-SCCAI)¹⁶, patient-HBI (p-HBI)¹⁷, Numeric Rating Scale (NRS)¹⁸, mobile health index (mHI)¹⁹, patient-reported outcome derived from the Mayo score (PRO2)²⁰, patient-reported outcome derived from the CDAI (PRO3)²¹, simple 0-10 numerical score (IBD-10)²², patient-reported HBI²³, patient-reported SCCAI²³, digital self-administered SCCAI^{24, 25}, digital self-administered HBI²⁵.

Study characteristics

An overview of the study characteristics, including the reasons for PROM development, is given in table 1. Included studies were conducted between 1999 and 2016 with study populations varying from 46 to 566 patients. Three studies included CD patients^{13, 17, 21}, eight included UC patients^{9-11, 14-16, 20, 24} and six included both CD and UC patients^{12, 18, 19, 22, 23, 25}. The majority of studies included only adult patients, whereas two included children in their studies^{14, 15}.

Table 1. Study characteristics of included articles investigating measurement properties of PROMs for IBD disease activity assessment.

Population	PROM	Aim of the study	N	Age (years, mean (SD))
Patients with UC	Self-administered SCCAI¹	To determine reliability and validity of the SCCAI when self-administered.	A: cross-sectional study - N=63 B: longitudinal study - N=191 C: segment of cohort A - N=68	A: 48 (15.9) B: 49 (13.4) C: 50 (14.1)
	6-point Mayo score and patients' assessment of disease activity²	To investigate what amount of change on the partial mayo score reflects a clinical meaningful change from the perception of the patient.	105	N/A
	Patients' global assessment¹⁵	To clarify whether a patient- or physician-based approach should be preferred when measuring disease activity in clinical studies.	A: children - N=94 B: adults - N=86	A: 11.8 (4.1) B: 37.6 (13.7)
	Patient-based PUCAI¹⁴	To determine the extent of agreement between patient- and physician-completed PUCAI scores and to validate these scores with other markers of disease activity.	70	14.3 (4.6)
	Patient-SCCAI¹⁶	To develop an easy to use patient-based SCCAI questionnaire to measure disease activity and to test agreement between the patient-SCCAI and the original clinician-based SCCAI.	149	Median 48 (range 37-59)
	6-point Mayo score¹⁰	To assess the correlation of the 6-point Mayo score with the SCCAI and patient-defined disease activity for use in clinical trials.	A: initial cohort - N=282 B: validation cohort - N=59	A: 47 (16) B: 39 (14)
	Patient-reported outcome derived from the Mayo score (PRO2)²⁸	To develop an interim PRO for use in clinical trials in UC to allow continuing evaluation of new therapies.	A: derivation cohort - N = 194 B: validation cohort - N = 181	A: - Intervention: 42.6 (14.3) - Placebo: 40.7 (13.8) B: - Intervention 1: 41.6 (14.6) - Intervention 2: 43.8 (14.6) - Placebo: 38.9 (13.4)
	Self-administered SCCAI²⁴	To evaluate the diagnostic performance of the SCCAI to assess UC activity when self-administered by the patient through a web platform compared with in-clinic assessment by the physician.	199	38
Patients with CD	Survey-index CDAI¹³	To develop a score that captures disease activity in patients not amenable to clinical assessment.	106	35 (N/A)
	Patient-HBI¹⁷	To develop an easy and undemanding patient-based questionnaire to measure CD activity and to test agreement between the patient-HBI and the original clinician-based HBI.	181	Median 41 (range 30-52)
	Patient-reported outcome derived from CDAI (PRO2 and PRO3)²¹	To generate an interim measure that can facilitate the continuing evaluation of new medical therapies until a new thoroughly developed and validated PRO is available.	A: development cohort - N=402 B: validation cohort - N=141	A: Placebo-med1-med2-med3 (median age) 37 (18-72) - median age 32 (18-66) - 34 (18-74) - 34 (18-73). B: 36 (11), 34 (10)

Female (%)	Disease duration (years, mean, (SD))	Disease activity at baseline	Risk of bias assessment
A: 51% B: 49% C: 53%	A: N/A B: N/A C: N/A	A: 43 remission, 25 relapse (11 mild, 11 moderate, 3 severe) B: N/A C: N/A	-
N/A	N/A	Mild to moderate defined as total DAI score of 4-10: Median baseline activity 7.0	Selection bias: only patients with mild to moderate disease activity at baseline (active disease) were included
A: 54% B: 48%	A: 1 (0.1-2.9) B: 6.6 (2.1-13.1)	A: remission 32%, mild 23%, moderate 31%, severe 14% B: remission 48%, mild 28%, moderate 18%, severe 4%	-
46%	26 months (N/A)	N/A	-
50.3% (n=75)	Median 12 (range 6-20 range)	According to CRP: 25 active, 49 remission According to PGA: 21 active, 25 remission	-
A: 59% B: 56%	A: <1yr: 1 1-5yr: 47 5-10yr: 76 >10yr: 152 B: <1yr: 0 1-5yr: 9 5-10yr: 18 >10yr: 32	Last active UC symptoms experienced A: -Within past 3 months: 98 -3-6 months ago: 27 -6 months to 1yr ago: 30 ->1yr ago: 113 B: N/A	-
A: - Intervention: 38.1% - Placebo: 42.5% B: - Intervention 1: 43.1% - Intervention 2: 50% - Placebo: 44.4% 56%	A: - Intervention: 55.6 ±75.1 months - Placebo: 52.8 ±76.4 months B: - Intervention 1: 78.0±84.9 months - Intervention 2: 74.8± 77.8 months - Placebo: 82.9±83.5 months N/A	100% of patients had mild to moderately active disease (UCDAI 4-10) 63.8% remission	Selection bias: only patients with mild to moderate disease activity at baseline (active disease) were included
61%	9 (3-15)	N/A	-
62.4% (n=113)	Median 12 (range 6-21)	N/A	-
A: Placebo-med1-med2-med3 59%-62%-54%-59% B: 45%-46%	N/A	100% of patients had mild to moderately active disease (CDAI≥150)	Selection bias: only patients with mild to moderate disease activity at baseline (active disease) were included

Table 1. Study characteristics of included articles investigating measurement properties of PROMs for IBD disease activity assessment. (*continued*)

Population	PROM	Aim of the study	N	Age (years, mean (SD))
Patients with UC and patients with CD	Manitoba Inflammatory Bowel Disease Index¹²	To propose a new self-report measure of disease activity.	353 (CD N=184, UC N=169)	41 (14.5)
	Numeric Rating Scale¹⁸	To assess the validity, reliability, and responsiveness of the NRS compared to disease activity indices, HRQOL measurements, and inflammatory markers.	A: prospective study - N=46 B: retrospective study - N=216 (CD N=135, UC N=81)	A: N/A B: CD 43 (N/A), UC 46 (N/A)
	Mobile Health Index¹⁹	To identify the most optimal PRO score to use on an IBD disease-monitoring app.	A: development cohort - N=219 (CD N=110, UC N=109) B: validation cohort - N=566 (CD N=301, UC N=265)	Median age (range) A: CD 33 (19-79), UC 35 (18-81) B: CD 33 (18-75), UC 42 (18-86)
	IBD-10²²	To assess the utility of a single-item patient-reported global disease control scale by comparing it to conventional clinical indices of disease activity.	405 (CD N=209, UC N=196)	41 [IQR 27-55yr]
	Patient-reported HBI en SCCAI²³	To better understand the relationship between patient-reported clinical disease activity indices and fecal calprotectin as measures of clinically active disease and mucosal inflammation.	356 (CD N=191, UC N=165)	CD: 46.7 (16.5) UC: 51.2 (16.3)
	Self-administered SCCAI and HBI²⁵	To compare a paper version of the SCCAI and HBI with their digital version with regard to total scores and number of missing answers.	128 (CD N=74, UC N=54)	UC: median 43 (range 19-74) CD: median 39 (range 14-78)

CD, Crohn's Disease; CDAI, Crohn's Disease Activity Index; CRP, C-reactive protein; HBI, Harvey Bradshaw Index; N/A, not available; NRS, numeric rating scale; PGA, physician global assessment; PROM, patient-reported outcome measure, PUCAI, Pediatric Ulcerative Colitis Activity, SCCAI, Simple Clinical Colitis Activity Index; SD, standard deviation; UC, ulcerative colitis.

Female (%)	Disease duration (years, mean, (SD))	Disease activity at baseline	Risk of bias assessment
59%	4.3 (2.1)	N/A	-
A: N/A B: 55%	A: N/A B: CD 13.5 (N/A), UC 10.2 (N/A)	N/A	-
A: 48% B: 51%	Median age (range) A: CD 8 (0-46), UC 6 (0-52) B: CD 8 (0-52), UC 7 (0-59)	Active disease defined as HBI>4 or Mayo>2 A: CD 30%, UC 37% B: CD 27%, UC 31%	-
54%	N/A	Remission defined as HBI≤4: 254 (63%) Remission defined as SCCAI≤2: 149 (37%)	The cut-off value for the IBD-10 was only internally validated (in the same cohort)
CD: 62.3% UC: 53.9%	N/A	Active disease defined as fecal calprotectin ≥250: CD 73 (38.2), UC 65 (39.4)	-
UC: 48% CD: 53%	N/A	N/A	-

Characteristics and measurement properties of PROMs

Characteristics of PROMs

Characteristics of the included patient-reported questionnaires are demonstrated in supplementary table 1. Three categories of PROMs could be identified: those derived from existing clinical activity scores, i.e. the SCCAI (n=5), the PUCAI (n=1), and the HBI (n=3), questionnaires using subcomponents of the Mayo Score (n=3) and the CDAI (n=2), and newly developed questionnaires (n=6).

Content validity

Since the main purpose of a PROM is to capture patients' perspectives, the FDA recommends patient input during instrument development. Two articles reported on patients' experiences regarding the tested PROM^{9,18}. However, only Bennebroek *et al.* documented qualitative patient interviews as part of the PROM development (table 2)^{16,17}.

Figure 1. Flowchart illustrating published studies included in the systematic review.

Construct validity

Seven articles investigated the correlation between clinician-reported indices and their patient-reported version (table 2). The SCCAI when self-administered by patients showed a high correlation and substantial to good agreement when compared to the clinician-reported version^{9,16}. The individual items “day-time frequency”, “night-time frequency” and “blood in stool” showed better agreement than the items on “urgency”, “well-being”, and “extra-intestinal manifestations”⁹. The self-administered SCCAI showed, however, a poor correlation with FC levels²³. Patient-based and clinician-based HBI-scores were also compared and showed a high correlation, but moderate agreement between the two questionnaires¹⁷. Additionally, the patient-reported HBI showed a poor correlation with FC levels (table 2). In children, Lee *et al.* found good agreement between the PUCAI when self-administered and when clinician-completed¹⁴. Compared to the physician’s global assessment, the self-administered PUCAI showed moderate agreement¹⁴. Both patient- and clinician-completed PUCAI scores did correlate moderately with CRP and substantially with ESR (table 2)¹⁴.

Two articles elaborated on the correlation between an online-administered questionnaire and a paper version (table 2). Both studies showed good agreement between the HBI and SCCAI filled out on paper and via a web tool^{24, 25}.

Five studies used subcomponents of a conventional clinical index to develop a new PROM. Three of these used the two patient-reported items from the Mayo score, i.e. stool frequency and rectal bleeding^{10,11,20}. These items combined showed an AUC of 0.80 when compared with the endoscopic modified Baron score²⁰, and strong correlations with the SCCAI¹⁰ and the full Mayo score¹¹ (table 2). Two articles composed a new PROM using the items stool frequency, abdominal pain and general wellbeing from the CDAI^{13,21}, showing moderate agreement and a relatively high correlation with the CDAI^{13,21} (table 2).

Six articles reported on the development and validation of a new PROM relative to conventional clinical indices and/or endoscopy (table 2)^{11, 12, 15, 18, 19, 22}. The MIBDI is a single-item self-reported question on symptom persistence in the previous 6 months. The MIBDI showed good sensitivity and modest specificity when compared with the HBI and the Powel Tuck Index¹². Lewis *et al.* asked patients to grade their current disease activity on a 6-point Likert scale from minimal symptoms to severe symptoms and found a moderate to strong correlation compared to the full Mayo score¹¹.

Three studies reported on a single-item numerical scale to capture disease activity for routine clinical use (table 2). The IBD-10, assessing “how would you rate your CD/UC today (on a scale of 0-10)”²², showed high correlation with the SCCAI and a moderate correlation with the HBI. Although a significant correlation was found between the IBD-10 and CRP in UC patients, no correlation was observed between the IBD-10 and CRP in CD patients, nor with FC in both UC and CD patients²². The 11-point NRS, capturing patients’ overall perception of health on a scale from 0 to 10, showed a high correla-

Table 2. Measurement properties of the included patient-reported questionnaires.

Population	PROM	Content validity	Construct validity	Criterion validity
Patients with UC	Self-administered SCCAI¹	Reported patient's experiences regarding tested PROM	Agreement of 83% between patients and clinicians considering relapse or remission of disease.	N/A
	6-point Mayo score and patients' assessment of disease activity²	N/A	Correlation of self-administered SCCAI and Seo-index: $r=0.79$, $p<0.01$ N/A	Correlation between 6-point Mayo and full Mayo $r=0.88$ ($p<0.0001$) Patients' assessment of disease activity (6-point Likert scale from minimal to severe disease symptoms) compared to full Mayo score: $r=0.71$ ($p<0.0001$)
	Patients' global assessment¹⁵	N/A	Correlation of patients' global assessment using VAS scale compared to: - PUCAI: $r=0.67$ - CRP: $r=0.34$ - Albumin: $r=-0.42$ - ESR: $r=0.39$ - Hb: $r=-0.24$	Correlation with endoscopic inflammation (Beattie's grading system): $r=0.52$ - Full Mayo score: $r=0.70$
	Patient-based PUCAI¹⁴	N/A	Agreement of self-administrated PUCAI compared to: - Clinician-completed PUCAI: $\kappa=0.78$ - Physician's global assessment: $\kappa=0.57$ Patient- and clinician completed PUCAI correlation with: - CRP: $r=0.50$ - ESR: $r=0.70$	N/A
	Patient-SCCAI¹⁶	Qualitative patient interviews: quick to complete and questions clear	Self-administered SCCAI compared to clinician-reported SCCAI: $r=0.79$, $\kappa=0.66$	N/A
	6-point Mayo score¹⁰	N/A	Correlation between patient-reported items of full Mayo score (stool frequency and rectal bleeding) and SCCAI: $r=0.71$	N/A
	Patient-reported outcome derived from the Mayo score (PRO2)²⁰	N/A		Patient-reported items of full Mayo score (stool frequency and rectal bleeding) showed an AUC of 0.80 compared with endoscopic modified Baron score and an AUC=0.80 when compared to Mayo endoscopic subscore.
	Self-administered SCCAI²⁴	N/A	Agreement online self-administered SCCAI and physicians administered SCCAI: $r=0.79$ - $\kappa=0.66$ regarding remission/active disease - NPV 94.5% - PPV 68.0% Agreement between patient and physician after 3 months and 6 months: respectively 80.8% and 89.3% ($p=0.027$)	N/A

Reliability	Ability to detect change	Ease of administration (number of items)	Utility in clinical practice ^a (max score: 8)	Utility in clinical trials ^b (max score: 5)
N/A	N/A	9 items, including extra-intestinal manifestations	2	1
N/A	N/A	6-point Mayo: 2 items Patients' assessment of disease activity: 1 item	6-point Mayo: 4 Patients' assessment of disease activity: 4	6-point Mayo: 1 Patients' assessment of disease activity: 1
N/A	N/A	1 item	4	2
N/A	N/A	6 items	2	1
N/A	N/A	9 items, including extra-intestinal manifestations	3	2
N/A	N/A	2 items	3	1
N/A	N/A	2 items	4	1
N/A	Responsiveness of online-administered SCCAI at 3 and 6 months: Percentage of agreement between physicians' assessment of disease activity measured with SCCAI: 82.6% ($\kappa=0.52$, $r=0.60$)	9 items, including extra-intestinal manifestations	2	1

Table 2. Measurement properties of the included patient-reported questionnaires. (continued)

Population	PROM	Content validity	Construct validity	Criterion validity
Patients with CD	<i>Survey-index CDAI</i> ¹³	N/A	Agreement between survey-index CDAI (stool frequency, abdominal pain, general wellbeing) and CDAI: $\kappa=0.57$	N/A
	<i>Patient-HBI</i> ¹⁷	Qualitative patient interviews: questions clear and easy to complete	Patient-based HBI compared to clinician-based HBI: $r=0.82$, $\kappa=0.52$	N/A
	<i>Patient-reported outcome derived from CDAI (PRO2 and PRO3)</i> ²¹	N/A	Correlation in case of CDAI ≤ 150 PRO2: $r=0.76$ PRO3: $r=0.89$	N/A
	<i>Manitoba Inflammatory Bowel Disease Index</i> ¹²	N/A	MIBDI compared after 0-12-24 months with HBI: Sensitivity: 88%-85%-84% Specificity: 51%-57%-66%	N/A
	<i>Numeric Rating Scale</i> ¹⁸	N/A	Powel Tuck Index: Sensitivity: 84%-82%-66% Specificity: 61%-68%-61% Correlation between NRS and: - CDAI: $r=0.77$ - HBI: $r=0.56$ - SCCAI: $r=0.50$ - CRP, ESR, - FCP: no correlation	N/A
	<i>Mobile Health Index</i> ¹⁹	N/A	Correlation of mHI-CD with: - CDAI: $r=0.75$, AUC=0.95 - HBI: $r=0.75$, AUC=0.90 Correlation of mHI-UC with: - Partial Mayo score: $r=0.71$, AUC=0.91	Compared to SES-CD: - CD: AUC=0.63, $r=0.30$ Compared to Mayo endoscopic subscore: - UC: AUC=0.82, $r=0.60$
	<i>IBD-10</i> ²²	N/A	Correlation of IBD-10 with: - SCCAI: $r=-0.79$ - HBI: $r=-0.69$ Neither IBD-10 nor conventional clinical disease activity indices were able to discriminate patients in remission as defined by FCP.	N/A
	<i>Patient-reported HBI en SCCAI</i> ²³	N/A	Patient-reported HBI ≥ 5 compared to FCP ≥ 250 : - Sensitivity: 38.4% - Specificity: 65.3% - PPV: 40.6% - NPV: 63.1% Patient-reported SCCAI ≥ 5 compared to FCP ≥ 250 : - Sensitivity: 52.3% - Specificity: 68.0% - PPV: 51.5% - NPV: 68.7%	N/A

Reliability	Ability to detect change	Ease of administration (number of items)	Utility in clinical practice ^a (max score: 8)	Utility in clinical trials ^b (max score: 5)
S-CDAI test-retest reliability after 2-6 weeks: intraclass correlation coefficient of 0.81.	Mean paired difference: Unchanged health (n=31): -23 (95%CI -48,1) Improved health (n=49): -88 (95%CI -119,-56) Deterioration (n=15): 22 (95%CI -39,84)	3 items	4	2
N/A	N/A	9-items, including extra- intestinal manifestations	3	2
N/A	PRO3 responsive to change with Guyatt responsiveness statistics of 0.49	PRO2: 2 item PRO3: 3 item	PRO2: 3 PRO3: 4	PRO2: 1 PRO3: 2
MIBDI test-retest reliability after 1 week: r=0.81 (95%CI 0.76- 0.86), κ=0.76 (95%CI 0.67-0.85)	N/A	1 item	3	2
N/A	Responsiveness (n=10) with mean between- questionnaire time of 108 days (range 24-243 days) Changes in patient-reported NRS did not correlate with changes in: - CDAI: r=0.20 - HBI: r=0.33	1 item	3	1
Test-retest reliability with a median time to second questionnaire of 22 hours: mHI-UC and mHI-CD intraclass correlation coefficient of 0.94	Significant difference in mHI-score between patients who clinically improved, remained stable or worsened (UC: p=0.0025; CD: p=0.0030) Tested in 50 patients with median between- questionnaire time of 46 days	mHI-CD: 4 items mHI-UC: 4 items	mHI-CD: 5 mHI-UC: 6	mHI-CD: 3 mHI-UC: 4
N/A	N/A	1 item	3	1
N/A	N/A	Patient-reported HBI: 7 items, including extra-intes- tinal manifestations Patient-reported SCCAI: 9 items, including extra- intestinal manifestations	Patient-reported HBI: 1 Patient-reported SCCAI: 1	Patient-reported HBI: 0 Patient-reported SCCAI: 0

Table 2. Measurement properties of the included patient-reported questionnaires. (continued)

Population	PROM	Content validity	Construct validity	Criterion validity
Patients with UC and patients with CD	Self-administered SCCAI and HBI ²⁵	N/A	Kappa-statistics of agreement online administered and paper-based questionnaire (o other conventional clinical activity indices)	N/A
			HBI: - Raw: 65% - Weighted: 97% SCCAI: - Raw: 78% - Weighted: 98%	

AUC, area under the curve; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FCP, fecal calprotectin; Hb, hemoglobin; HBI, Harvey Bradshaw Index, IBD, inflammatory bowel disease; mHI, Mobile Health Index; ICC, intra class correlation coefficient; MIBDI, Manitoba Inflammatory Bowel Disease Index; N/A, not available; NPV, negative predictive value; NRS, Numeric Rating Scale; PPV, positive predictive value; PROM, patient-reported outcome measure; PUCAI, Pediatric Ulcerative Colitis Activity Index; SCCAI, Simple Clinical Colitis Activity Index; SES-CD, Simple Endoscopic Score for CD; UC, ulcerative colitis; VAS, visual analog scale.

^a Indication for utility in clinical practice, judged on content validity (patient interviews = 1), construct validity ($p \geq 0.70/\kappa \geq 0.60/AUC \geq 0.70/sens \geq 80\%/spec \geq 80\% = 1$), criterion validity ($p \geq 0.70/\kappa \geq 0.60/AUC \geq 0.70/sens \geq 80\%/spec \geq 80\% = 2$), reliability ($p \geq 0.70/\kappa \geq 0.60/ICC > 0.80 = 1$), responsiveness ($p \geq 0.70/\kappa \geq 0.60/other$ measures of responsiveness = 1), ease of administration (≤ 5 items/no questions on extra-intestinal manifestations = 1), recall period (≤ 1 week = 1).

^b Indication for utility in clinical trials, judged on FDA criteria (i.e. content validity (patient interviews = 1), construct validity ($p \geq 0.70/\kappa \geq 0.60/AUC \geq 0.70/sens \geq 80\%/spec \geq 80\% = 1$), criterion validity ($p \geq 0.70/\kappa \geq 0.60/AUC \geq 0.70/sens \geq 80\%/spec \geq 80\% = 1$), reliability ($p \geq 0.70/\kappa \geq 0.60/ICC > 0.80 = 1$), responsiveness ($p \geq 0.70/\kappa \geq 0.60/other$ measures of responsiveness = 1)).

Reliability	Ability to detect change	Ease of administration (number of items)	Utility in clinical practice ^a (max score: 8)	Utility in clinical trials ^b (max score: 5)
N/A	N/A	Patient-reported HBI: 7 items	Patient-reported HBI: 2	Patient-reported HBI: 1
		Patient-reported SCCAI: 9 items	Patient-reported SCCAI: 2	Patient-reported SCCAI: 1

tion with the CDAI, moderate correlation with the HBI and no correlation with CRP, ESR and FC¹⁸. The latter study also tested a single-item self-reported question (yes/no) on remission of the disease and found a correlation with the CDAI and HBI, but not with CRP¹⁸. A third study reported on a single-item question about patient-reported disease activity during the previous 2 days on a VAS-scale¹⁵. This “patient global assessment” was compared to the full mayo score, the PUCAI score, CRP, albumin, ESR and hemoglobin, showing correlation coefficients of 0.70, 0.67, 0.34, -0.42, 0.39, and -0.24, respectively¹⁵.

Van Deen *et al.* developed and validated a PROM to monitor disease activity for use in mobile technologies (table 2). The mHI showed high correlation and high accuracy compared with the CDAI and the HBI for CD patients. Also for UC patients, the mHI showed high correlation and high accuracy compared to the partial Mayo score¹⁹.

Criterion validity

Only four articles reported on validation relative to endoscopic disease activity (table 2). The patient global assessment showed a moderate correlation with endoscopic inflammation scored with Beattie’s grading system¹⁵. The single-item “patient assessment of disease activity” and the 6-point Mayo score showed high correlation with the full Mayo score¹¹. Jairath *et al.* reported an AUC of 0.80 for the two-item (PRO2) Mayo score compared to the Mayo endoscopic subscore²⁰. The mHI-UC showed moderate accuracy in detecting mucosal inflammation compared to the Mayo endoscopic subscore, while the mHI-CD showed poor accuracy identifying patients with active disease compared to the simple endoscopic score for CD (SES-CD)¹⁹.

Reliability

Three articles investigated this test-retest reliability (table 2). The MIBDI showed strong test-retest reliability when the question was re-administered after 1 week, with high correlation between the two MIBDI scores and good agreement for active versus inactive categorization at the two measurement occasions¹². The S-CDAI was reliable when re-administered after 2-6 weeks as shown by an intraclass correlation coefficient of 0.81¹³.

For both the mHI-UC and mHI-CD, the intraclass correlation coefficient was 0.94 with a median time to second questionnaire of 22 hours¹⁹.

Responsiveness

Ability to detect changes in disease activity (responsiveness) was tested in five studies (table 2). Timmer *et al.* reported good ability to detect change for the S-CDAI as the mean paired difference was different for patients whose disease activity improved or deteriorated; effect size statistics were not applied¹³. Surti *et al.* tested responsiveness of the NRS in 10 patients with a mean between-questionnaire time of 108 days. Changes in NRS did not correlate with changes in CDAI and HBI¹⁸. Van Deen *et al.* assessed sensitivity to detect change in a subset of 50 patients with a median between-questionnaire time of 46 days and found a significant difference in mHI-score between patients who clinically improved, remained stable or worsened¹⁹. Khanna *et al.* found their PRO3 derived from the CDAI to be responsive to change²¹. Marín-Jiménez *et al.* tested the responsiveness of online-administered SCCAI at 3 and at 6 months. The percentage of agreement with the physicians' assessment of disease activity measured with the SCCAI was 82.6% with a moderate correlation between the two questionnaires²⁶.

DISCUSSION

In addition to the increasing focus on patient-centered care, tight monitoring of IBD disease activity is advocated to improve long-term disease outcome. This systematic review provides an overview on the current available patient-reported outcome measures for measurement of IBD disease activity based on their measurement properties. A wide variety of PROMs has been developed, but none of these meet all the criteria for PROM-development as recommended by the FDA⁸.

The adequacy and accuracy of a PROM extensively depend on its content- and on its criterion validity. As a PROM is aimed at the reflection of what is important to patients, evaluation of the completeness of item coverage, but also of its comprehensiveness, clarity and readability is crucial. Asking patients about their general well-being, for example, might be too susceptible for different interpretations for reliable assessment of IBD disease activity⁸. Patients might also experience difficulties in understanding of extra-intestinal manifestations, in interpretation of liquid or loose stools since they lack standardisation, and in examination of the presence of an abdominal mass. Furthermore, pain measurement on a four-point scale, for example, might be less suitable than on a visual analog scale, since response options need to offer a clear distinction between choices and should measure relevant nuances. The input of patients is especially important when PROMs are used to "value" health systems or interventions. However, patient

input during development was only carried out in two articles (patient-HBI and patient-SCCAI)^{16, 17}. In addition, four of the reviewed PROMs comprise of one single question on current disease activity. As IBD disease activity is thought to manifest with a wide variety of symptoms, it could be discussed if a PROM consisting of one single global question captures all aspects of the complex process of disease activity. However, these single-items PROMs show comparable accuracy relative to the conventional clinical indices as the multi-item PROMs.

For a PROM measuring disease activity, validation relative to the golden standard, which is endoscopy for IBD activity, is important. Only six PROMs were validated relative to endoscopy and showed moderate accuracy for detection of mucosal inflammation in UC patients and low accuracy in CD patients (patients' global assessment, patient assessment of disease-activity, mHI-CD, mHI-UC, PRO2 and 6-point Mayo score)^{11, 15, 19, 20}. Due to the fact that the development and validation of a new comprehensive PROM might take several years, many PROMs were derived or modified from existing clinical activity scores and validated relative to the original scores, and not to endoscopy. The mHI-UC and mHI-CD were newly developed based on correlation coefficients between individual questions from different available clinical activity scores with the partial Mayo score and HBI respectively. The likelihood of establishing a PROM which reflects mucosal inflammation with a high accuracy may however increase when the selection of individual questions is driven by the correlation of these questions with endoscopic findings. For UC, for instance, rectal bleeding and to a lesser extent stool frequency were found to be essential in a UC-PROM^{20, 27}. Nevertheless, it remains challenging to develop an accurate PROM as 20% of UC patients in clinical remission still have endoscopic disease activity, whereas endoscopic healing is not always accompanied by normalisation of stool frequency^{28, 29}. For CD patients, even up to 50% of patients in clinical remission still have mucosal inflammation³⁰.

The best patient-reported disease activity measure for a given situation may depend on research or clinical goals. For serial monitoring of disease activity in the context of tight control, high accuracy of a PROM compared to endoscopy is crucial. Specifically, such a disease activity index should have a high sensitivity, even if at the cost of false-positive results. In addition, ease of administration, a short recall period, and a good reliability and responsiveness to changes in disease activity are important for use in clinical practice. In this regard, the mHI-UC shows adequate measurement properties for assessing disease activity in UC patients^{19, 20}. For CD patients, no PROM which accurately reflects endoscopic disease activity is available. For registration of a patients' perspective on disease activity at fixed time-points or over a certain period, use of the single-item Manitoba IBD Index, asking patients about their disease activity over the past 6 months, could be convenient. In clinical trials, on the other hand, a PROM which

is consistent with guidance from the FDA might be first choice. However, none of the reviewed PROMs meet all the FDA criteria.

In this review we provided an overview of the available PROMs for IBD disease activity assessment. None of the available PROMs meet all the criteria for PROM-development as recommended by the FDA. For the majority of PROMs, information on their correlation with endoscopy is lacking and their utility to predict mucosal inflammation remains therefore unclear. The few articles that reported on criterion validity showed low to moderate accuracy in identifying IBD patients at risk for active disease. In addition, only a minority of PROMs reported patient-input during its development which is crucial as PROMs are aimed at capturing patients' perspectives. With an increasing demand for use of PROMs in routine practice, clinical trials, telemedicine systems and value-based healthcare programs, there is an urgent need on data regarding the content and criterion validity of the available PROMs.

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Supplementary table 1. Characteristics of the included PROMs.

Intended population	PROM	Language	Items	Administration mode	Recall period	Scoring and cut-off
UC patients	Self-administered SCCAI⁹	English	Bowel frequency during day and night, urgency, blood in stool, general well-being, extra colonic manifestations (including photographs illustrating extra-intestinal manifestations)	Paper	N/A	SCCAI: > 5 points is relapse
	6-point Mayo score and patients' assessment of disease activity¹¹	English	Patient assessment of clinical activity: perfect, minimal, mild, moderate, moderately severe, severe 6-Point Mayo: stool frequency, rectal bleeding	N/A N/A N/A	N/A	1. 4-5 points of full Mayo with sensitivity 88% and specificity 78% (ROC =0.85) 2. 2.5 points of full Mayo with sensitivity 71% and specificity 84% (ROC =0.85) 3. 1.5 of full Mayo with sensitivity 65% and specificity 81% (ROC =0.78) N/A
	Patients' global assessment¹⁵	English	How do you feel with regard to your colitis during on a VAS-scale?	Paper	Past 2 days	N/A
	Patient-based PUCAI¹⁴	English	Abdominal pain, rectal bleeding, stool consistency, stool frequency, nocturnal stools, activity level	Paper	Past 2 days	PUCAI: <10 inactive disease, 10-34 mild disease, 35-64 moderate disease, 65-85 severe disease
	Patient-SCCAI¹⁶	Dutch	Patient-reported SCCAI: Stool frequency, nocturnal stools, urgency, adjustments in daily activities, incontinence, blood in stool, general well-being, extra-intestinal manifestations; arthralgia, red or swollen joints, woken up at night from arthralgia, erythema nodosum, pyoderma gangrenosum, uveitis	Paper	Previous week	SCCAI: ≥ 5 is active disease
	6-point Mayo score¹⁰	English	6point mayo: stool frequency, rectal bleeding	Paper	N/A	1. 6-point Mayo: <1.5 is remission
	Patient-reported outcome derived from the Mayo score (PRO)²⁰	English	Rectal bleeding, stool frequency	N/A	N/A	Remission: bleeding = 0, bowel frequency ≤2
	Self-administered SCCAI²⁴	Spanish	Patient-reported SCCAI: Bowel frequency during day and night, urgency, blood in stool, general well-being, extra colonic manifestations (including photographs illustrating extra-intestinal manifestations)	Digital	N/A	SCCAI: > 2 is active disease
	Survey-index CDAI¹³	German	General wellbeing, abdominal pain, stool frequency	Paper	N/A	N/A
	Patient-HBI¹⁷	Dutch	Patient-reported HBI: General wellbeing, abdominal pain, frequency loose stools, extra-intestinal manifestations; arthralgia, uveitis, erythema nodosum, pyoderma gangrenosum, aphthous ulcer, anal fissure, active fistula or abscess	Paper	Previous week	HBI: ≥5 is active disease
CD patients	Patient-reported outcome derived from CDAI (PRO2 and PRO3)²¹	English	PRO 2: number of liquid or very loose stools, abdominal pain PRO 3: number of liquid or very loose stools, abdominal pain, general well-being	N/A	Past 7 days	Remission: stool frequency mean daily score ≤1.5, abdominal mean daily score ≤1 and general well-being score ≤1

Supplementary table 1. Characteristics of the included PROMs. (continued)

Intended population	PROM	Language	Items	Administration mode	Recall period	Scoring and cut-off
Both UC and CD patients	<i>Manitoba Inflammatory Bowel Disease Index</i> ¹²	English	In the following 6 months my disease has been a) constantly active, symptoms every day, b) often active, symptoms most days, c) sometimes active, symptoms some days, d) occasionally active, symptoms 1-2 days/month, e) rarely active, symptoms few days past 6 months, f) no symptoms what I consider remission or absence of symptoms	N/A	Previous 6 months	Response a – d considered active disease. Response e-f considered remission.
	<i>Numeric Rating Scale</i> ¹⁸	English	VAS-scale to evaluate health status: 0 = as bad as being dead, 10 = perfect health	N/A	Past 24 hours and past 7 days	Remission rated by separate yes/no question "Do you feel your disease is in remission?"
	<i>Mobile Health Index</i> ¹⁹	English and Dutch	MHI-CD: liquid/soft stools/day (0, 1-2, >3), abdominal pain yes/no, well-being 0-10, disease control 0-10	Digital	24 hours	Active disease according to MHI: CD>5.5, UC>4.99
	<i>IBD-10</i> ²²	English	MHI-UC: stools yesterday, abdominal pain 0-10, rectal bleeding 0-10, disease control 0-10 On a scale of 0 to 10, 10 being the best, how would you rate your Crohn's disease/ulcerative colitis today?	Verbally answered	24 hours	IBD-10: ≥ 7 predicts remission
	<i>Patient-reported HBI</i> and <i>SCCAI</i> ²³	English	Patient-reported HBI: General well-being, abdominal pain, frequency loose stools, extra-colonic manifestations	N/A	N/A	HBI and SCCAI: ≥ 5 is clinical active disease
<i>Self-administered SCCAI and HBI</i> ²⁵	Danish		Patient-reported SCCAI: Bowel frequency during day and night, urgency, blood in stool, general well-being, extra colonic manifestations	Paper and digital	N/A	N/A
			Patient-reported HBI: General well-being, abdominal pain, frequency loose stools, extra-colonic manifestations			
			Patient-reported SCCAI: Bowel frequency during day and night, urgency, blood in stool, general well-being, extra colonic manifestations (including photographs illustrating extra-intestinal manifestations)	Paper and digital		
			Patient-reported SCCAI: Bowel frequency during day and night, urgency, blood in stool, general well-being, extra colonic manifestations (including photographs illustrating extra-intestinal manifestations)			

PROM; patient-reported outcome measure; N/A, Not available; CD, Crohn's Disease; UC, ulcerative colitis; SCCAI, Simple Clinical Colitis Activity Index; CDAI, Crohn's Disease Activity Index; HBI, Harvey Bradshaw Index; CRP, c-reactive protein; ROC, receiver operating characteristic; IBDQ, Inflammatory Bowel Disease Questionnaire; Hb, hemoglobin; 5-ASA, 5-aminosalicylic acid; MHI, Mobile Health Index.

Chapter 3

Development and validation of a patient-reported score to screen for mucosal inflammation in inflammatory bowel disease

Marin de Jong, Danielle Roosen, Juliette Degens, Tim van den Heuvel,
Marielle Romberg – Camps, Wim Hameeteman, Alexander Bodelier,
Igor Romanko, Milan Lukas, Bjorn Winkens, Tineke Markus,
Ad Masclee, Astrid van Tubergen, Daisy Jonkers, Marieke Pierik

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ABSTRACT

Background: Patient-reported outcome measures (PROMs) assessing inflammatory bowel disease (IBD) activity are of interest for monitoring in clinical practice, telemedicine systems or trials. Different PROMs for follow-up of disease activity are available; however, none was developed with endoscopy as golden standard. The objective of this study was to develop and validate a PROM to predict endoscopic disease activity following the recommendations of the Food and Drug Administration.

Methods: During development, 178 IBD patients undergoing a colonoscopy were asked to fill out 13 clinical questions derived from the literature. During endoscopy, inflammation was assessed with the simplified endoscopic score for Crohn's disease (CD) and the Mayo endoscopic subscore for ulcerative colitis (UC). Based on correlation with endoscopic inflammation, questions were reduced to a total of 6 for CD and 5 for UC. The newly developed Monitor IBD At Home questionnaire (MIAH) was validated in an independent cohort of 135 CD and 131 UC patients. Additionally, diagnostic accuracy of the MIAH combined with a fecal calprotectin home-test was assessed.

Results: The MIAH-CD includes questions on rectal bleeding, mucus, stool frequency, urgency, fatigue and patient-reported disease activity. The MIAH-UC contains items on rectal bleeding, stool frequency, urgency, abdominal pain and patient-reported disease activity. Both questionnaires showed to be valid, reliable, and responsive to changes. The MIAH and fecal calprotectin home-test combined had a sensitivity, specificity, NPV and PPV of 96.7%, 66.7%, 94.7%, and 76.3% for CD and of 88.2%, 81.4%, 95.6%, 60.0% for UC, compared to endoscopy.

Conclusion: The MIAH is the first PROM developed to predict endoscopic inflammation in IBD patients. A combination of this questionnaire and a fecal calprotectin home-test shows excellent diagnostic accuracy to screen for patients who need further assessment of disease activity and can be used in daily practice, telemedicine systems and trials.

INTRODUCTION

Inflammatory bowel diseases (IBD), which include Crohn's disease (CD) and ulcerative colitis (UC), are chronic relapsing inflammatory diseases of the gastrointestinal tract. They vary widely among individuals with regard to the clinical presentation, disease location and behaviour, frequency of relapses, and occurrence of extra-intestinal manifestations¹. Over the past years, strategies for management of IBD have shifted from mere management of symptoms towards tight control of mucosal inflammation and personalised monitoring to improve long-term outcomes and quality of life²⁻⁶.

Close disease monitoring is challenging in a traditional healthcare setting with limited medical and financial resources and more so since the incidence of IBD is increasing^{7,8}. Patient-reported outcome measures (PROMs) used for symptom management, for instance incorporated in telemedicine systems, assist healthcare professionals to implement such a tight control strategy in IBD patients. In addition, use of PROMs is increasingly advocated as a means of supporting patient-centered care, in outcome measurement and in quality improvement^{9,10}.

In the context of tight control, PROMs monitoring IBD activity should accurately reflect mucosal inflammation. Different PROMs have been developed for follow-up of disease activity in clinical trials and clinical practice, such as the Manitoba IBD Index¹¹, the single-item numeric rating scale¹², the simple 0-10 numerical score¹³, the mHealth index¹⁴ and questionnaires derived from the Harvey Bradshaw Index (HBI)¹⁵⁻¹⁷, the Simple Clinical Colitis Activity Index (SCCAI)¹⁶⁻²⁰, the Crohn's Disease Activity Index (CDAI)^{21,22} and the Mayo Clinic Score (MCS)²³⁻²⁵.

In order to develop an accurate PROM, content validity, construct validity, criterion validity, reliability and the ability to detect changes over time should be addressed, according to recommendations of the Food and Drug Administration (FDA)^{26,27}. However, the PROMs developed to assess disease activity in IBD were generally not developed according these recommendations. Especially use of endoscopy as gold standard was lacking.

Therefore, we aimed to develop a new PROM for remote monitoring following the recommendations for PROM development from the FDA²⁶ and validate this PROM relative to endoscopy.

METHODS

Design

This prospective, observational study was designed in three phases: a development and a validation phase of a new PROM, the Monitor IBD At Home (MIAH) questionnaire, and

a third phase in which the MIAH was tested in combination with a fecal calprotectin (FC) home-test, together referred to as the MIAH score.

Development phase

To develop a new PROM for mucosal inflammation in CD and UC, all questions from available patient-reported disease activity scores were collected from the literature²⁸. Of these, thirteen patient-reported questions regarding disease activity in IBD were selected by an expert panel (MP, WH, MR, AB) (supplementary table 1 and 2). Questions on extra-intestinal manifestations were excluded and in case of overlapping questions, the question with the clearest wording was selected. Between March 2013 and July 2014, consecutive IBD patients with a scheduled routine endoscopy at Maastricht University Medical Center+ (MUMC+), were invited to fill out this 13-item questionnaire before start of bowel cleansing. Patients with a medical history of extensive bowel surgery as an ileostomy, colostomy, ileoanal pouch anastomosis or ileorectal anastomosis were excluded as they require separate scoring. During endoscopy, mucosal inflammation was assessed by a trained endoscopist with the simplified endoscopic score (SES-CD) for CD or the Mayo endoscopic subscore (MES) for UC. An independent blinded gastroenterologist (MP) reviewed all endoscopic reports and images and video material if available. In case of disagreement, the independent gastroenterologist and endoscopist discussed the findings to reach consensus.

Spearman correlation coefficients were calculated between each of the 13 individual items and endoscopic disease activity. Based on these correlations and supported by expert opinion, a selection of best correlating items without overlap between the items was made and combined into four domains. We then performed a multivariable logistic regression analysis, using the items within one domain as independent variables and endoscopic disease activity as dependent variable, to form a scoring algorithm within each domain. The intra-domain weight factor (table 2) was then set equal to the regression coefficient of that item divided by the sum of the regression coefficients of the items to make sure that the weight factors within a domain add up to 1. As a next step, multivariable logistic regression, using the four domains as independent variables and endoscopic disease activity as dependent variable, was performed. Receiver-operator characteristics (ROC) curves were used to determine the best cut-off value for the predicted probability of having endoscopic disease activity. Because the main aim was to identify patients at risk for active disease, we defined the optimal cut-off for disease activity as the one with the highest specificity of those with a sensitivity of at least 85% and negative predicted value (NPV) of at least 95%. A scoring algorithm was formed using the regression coefficients of independent predictors in the multivariable model.

After selection of relevant questions, qualitative cognitive interviews with 10 IBD outpatients were planned to check clarity, readability, intelligibility and completeness

of the questionnaire. Based on these interviews, questions, response options and recall period were optimized if necessary.

Validation phase

In order to investigate the score's measurement properties, i.e. criterion validity, reliability and ability to detect change, a validation cohort was formed. Between March 2015 and December 2016, adult consecutive IBD patients with a scheduled routine endoscopy at the MUMC+, Zuyderland Medical Center Sittard (ZMC) and Amphia Hospital Breda (AH), were eligible for inclusion. Patients with an ileostomy, colostomy, or ileoanal pouch anastomosis were again excluded. Eligible patients were invited to fill out the 5-item MIAH-UC questionnaire for UC or the 6-item MIAH-CD questionnaire for CD prior to bowel cleansing. During endoscopy, mucosal inflammation was scored with the SES-CD and the MES by trained endoscopists and again reviewed by an independent gastroenterologist. Criterion validity was evaluated by calculation of the MIAH questionnaires' sensitivity, specificity, positive predictive value (PPV) and NPV using the endoscopic activity scores as standard. To evaluate test-retest reliability, a subset of consecutive stable outpatients, i.e. no change in clinical situation or treatment, was asked to fill out the MIAH questionnaire during an outpatient visit and a second time at home within one week after the outpatient visit. Test-retest reliability of the MIAH questionnaires was assessed by the intra-class correlation coefficient (ICC). The score's ability to detect disease activity over time was assessed by inclusion of a subset of 54 patients from both the development and the validation cohort who underwent two routine endoscopies within the study period. The MIAH scores of patients who endoscopically improved, remained stable and deteriorated were compared with a Kruskal-Wallis test (i.e. the Kruskal Wallis test is the non-parametric alternative to the one way anova and determines whether the medians of two or more groups are different).

Fecal calprotectin substudy

A total of 109 patients from the validation cohort were asked to collect a stool sample prior to bowel cleansing. In this sample, FC was assessed with two different FC home-tests and by the routine laboratory test of the MUMC+. These FC home-tests were the first ones available for commercial use. During the study period the tests were performed by the researchers to minimise test variability. Pearson correlation coefficients between the FC home-test values and FC routine laboratory measurements were calculated. To determine the optimal cut-off for the FC home-tests for predicting endoscopic disease activity, ROC curves were generated. We defined the optimal cut-off for disease activity as the one with the highest specificity of those with a sensitivity of at least 80%.

To assess diagnostic accuracy of the MIAH-UC and MIAH-CD in combination with the FC home-tests, sensitivity, specificity, PPV and NPV were calculated using endoscopic scores as standard.

Measurements

Endoscopy

For CD patients, endoscopic disease activity was defined as an SES-CD score ≥ 2 . For UC patients, endoscopic disease activity was defined as a MES >1 . Endoscopic scoring was performed by a trained endoscopist. A second gastroenterologist independently scored mucosal inflammation based on reports, images and video material if available. In case of a disagreement in scores, the final decision was made through discussion and consensus.

Fecal calprotectin

Fecal calprotectin was measured using two different home-tests (QuantOn Cal (QoC)[®] (Preventis, Germany) and Calpro Smart (CS)[®] (CalproAS, Norway)) and by the routine laboratory test (Phadia[®]) of the MUMC+. Both FC home-tests consisted of an extraction kit with a dosing tip and a lateral flow device and were performed following manufacturer's instructions; the dosing tip was dipped 3-5 times into the stool to ensure homogeneity after which the dosing tip was transferred to the test tube with prefilled extraction fluid. The test tube was shaken to mix the stool with the fluid and a few drops were applied to the sample window of the lateral flow device and left for 15 minutes incubation. Finally, a picture of the lateral flow device was made with a smartphone, after which a test result was calculated. The lower and upper limits for FC detection were 25 and 2000 $\mu\text{g/g}$ for the QuantOn Cal test and 70 and 1500 $\mu\text{g/g}$ for the Calpro Smart test.

Statistical analyses

All described analyses were performed using IBM SPSS statistics 22.0. A two-sided p-value ≤ 0.05 was defined as statistically significant.

Ethical considerations

The study was approved by the Medical Research Ethics Committee of the Maastricht University Medical Center+. This approval was applicable to all participating centers. All patients gave written informed consent prior to participation.

RESULTS

Development phase

During the development phase, 98 CD patients and 80 UC patients were included. Base-line characteristics are shown in table 1. In addition, 10 outpatients participated in the qualitative interviews to ensure content validity of the questionnaire. Patients judged the single questions on clarity, readability, intelligibility and completeness until saturation was reached. Patients indicated to prefer questions with a recall period of 24 hours over questions with a longer recall period and numeric rating scales or yes/no answers

Table 1. Patient characteristics.

	Development phase		Validation phase		Fecal calprotectin substudy	
	CD (n=98)	UC (n=80)	CD (n=135)	UC (n=131)	CD (n=57)	UC (n=52)
Age (years), mean (SD)	44.7 (14.2)	52.2 (15.3)	47.7 (14.2)	52.2 (15.7)	50.6 (14.0)	56.6 (12.4)
Male, N (%)	41 (41.8)	47 (58.8%)	56 (41.5)	75 (57.3)	27 (47.4)	30 (57.7)
Age at diagnosis, mean (SD)	29.4 (13.1)	38.3 (16.4)	32.4 (12.6)	38.0 (15.1)	32.7 (13.4)	41.3 (14.5)
Disease duration (years), mean (SD)	15.4 (11.6)	13.3 (12.6)	14.9 (11.2)	13.5 (10.3)	17.6 (10.5)	15.5 (10.2)
Phenotype, N (%)						
Localisation						
E1 Proctitis	N/A	15 (18.8)	N/A	7 (5.3)	N/A	0 (0)
E2 Left sided	N/A	44 (55.0)	N/A	74 (56.5)	N/A	32 (61.5)
E3 Extensive	N/A	21 (26.2)	N/A	50 (38.2)	N/A	20 (38.5)
L1 Ileal	24 (24.5)	N/A	34 (25.2)	N/A	18 (31.6)	N/A
L2 Ileocolonic	30 (30.6)	N/A	40 (29.6)	N/A	20 (35.1)	N/A
L3 Colonic	44 (44.9)	N/A	61 (45.2)	N/A	19 (33.3)	N/A
L4 Upper GI	10 (10.2)	N/A	6 (4.4)	N/A	2 (3.5)	N/A
Behaviour						
B1 Non-penetrating, non-stricturing	67 (68.4)	N/A	90 (66.7)	N/A	36 (63.2)	N/A
B2 Stricturing	19 (19.4)	N/A	27 (20.0)	N/A	13 (22.8)	N/A
B3 Penetrating	12 (12.2)	N/A	18 (13.3)	N/A	8 (14.0)	N/A
Perianal disease	30 (30.6)	N/A	35 (25.9)	N/A	15 (26.3)	N/A
Treatment, N (%)						
No medication/5-ASA	NC	NC	44 (32.6)	60 (45.8)	18 (31.6)	20 (38.5)
Immunosuppressives	NC	NC	33 (24.4)	37 (28.2)	15 (26.3)	13 (25.0)
Biologicals or combination therapy	NC	NC	58 (43.0)	34 (26.0)	24 (42.1)	19 (36.5)
Surgical history, N (%)†	39 (39.8)	5 (6.2)	49 (36.6)	7 (5.3)	24 (42.1)	3 (5.8)
Active disease, N (%)	54 (55.1)	27 (33.8)	62 (44.9)	44 (33.6)	30 (52.6)	17 (32.7)

CD, Crohn's Disease; UC, ulcerative colitis; GI, gastro-intestinal; 5-ASA, 5-aminosalicylic acid; N/A, not applicable; NC, not collected; † ileocecal resection, hemicolectomy or sigmoid resection.

over categorical response options. The question on “liquid or soft stool frequency” was found to be hard to interpret, as patients judged “liquid or soft” during these interviews with Bristol Stool Scale ratings ranging from 4 to 7. Therefore and because of its lower correlation with endoscopic disease activity, we decided to exclude the question on “liquid or soft stools” and include a more general question on stool frequency (supplementary table 1 and 2). All numeric rating scales, i.e. on patient-reported disease activity, abdominal pain, and fatigue, were adjusted in the same direction, namely 0 as very poor and 10 as very well. The response options from the urgency-question were extended on patients’ advice from “yes/no” to “no”, “yes, urgent”, and “yes, very urgent”, to offer a clear distinction between choices.

For CD, patient-reported disease activity (domain 1), and questions on rectal bleeding and mucus loss (domain 2), stool frequency (domain 3), urgency and fatigue (domain 4) were selected as best predicting endoscopic disease activity (table 2), with an area under the curve (AUC) of 0.72 (figure 1A). The optimal cut-off value for the MIAH-CD was set at 3.6, resulting in a sensitivity of 90.4% and specificity of 40.9%. For UC, patient-reported disease activity (domain 1), and questions on rectal bleeding (domain 2), stool frequency (domain 3), urgency and abdominal pain (domain 4) were selected as best predicting endoscopic disease activity (table 2), with an AUC of 0.81 (figure 1B). The optimal cut-off for the MIAH-UC was set at 3.5, resulting in a sensitivity and specificity of 92.6% and 67.9%, respectively.

Table 2. Domains and individual items of the MIAH-CD and MIAH-UC questionnaire.

Domain	MIAH-CD items	Intra-domain weight factor	Inter-domain weight factor	MIAH-UC items	Intra-domain weight factor	Inter-domain weight factor
1	Patient-reported disease activity	1	0.096	Patient-reported disease activity	1	0.160
2	Rectal bleeding Mucus loss	0.4 0.6	0.097	Rectal bleeding	1	2.103
3	Stool frequency	1	0.184	Stool frequency	1	0.167
4	Urgency Fatigue	0.7 0.3	0.022	Urgency Abdominal pain	0.5 0.5	0.184

CD, Crohn’s disease; UC, ulcerative colitis; MIAH, Monitor IBD At Home.

Validation phase

During the validation phase, MIAH questionnaires from 135 CD patients (120 MUMC+, 7 ZMC, 8 AH) and 131 UC patients (116 MUMC+, 11 ZMC, 4 AH) were collected and analysed relative to endoscopic disease activity scores. Patient characteristics are shown in table 1. Using the preset cut-off of 3.6, the MIAH-CD showed a sensitivity of 67.6%, specificity of 81.3%, PPV of 69.3%, and NPV of 80.0% (table 3 and supplementary table 3). Using the cut-off of 3.5, the MIAH-UC showed a sensitivity of 68.2%, specificity of 80.5%, PPV of 63.8%, and NPV of 83.3% (table 3 and supplementary table 3). The test-retest reliability

was assessed in a subset of 20 CD and 7 UC patients. In CD patients, the ICC was 0.81 (95% CI 0.52–0.93) and for UC patients the ICC was 0.88 (95% CI 0.27–0.98). The ability to detect disease activity was assessed in a subset of 29 CD and 25 UC patients with a mean between-endoscopies period of 19.1 ± 11.1 months. In total, 15 patients deteriorated (27.8%), 24 patients had stable disease activity (44.4%), and 15 patients improved over time (27.8%). The MIAH score differed significantly over time between patients who clinically improved, remained stable or worsened ($p < 0.001$).

Fecal calprotectin substudy

As the overall sensitivity scores were rather low, we evaluated the addition of a FC home-test to the MIAH questionnaire in 109 patients (57 CD and 52 UC) (table 1). For CD patients, ROC curve analysis for the QOC FC home-test compared to endoscopy revealed an AUC of 0.82 (figure 2A). An optimal cut-off level of 100 $\mu\text{g/g}$ resulted in a sensitivity of 80.0% and a specificity of 70.4%. The CS FC home-test revealed an AUC of 0.75 (figure 2A). The optimal cut-off level of 100 $\mu\text{g/g}$ resulted in a sensitivity of 76.9% and a specificity of 58.3%. For UC patients, ROC curve analysis for the QOC FC home-test compared to endoscopy revealed an AUC of 0.84 (figure 2B), with an optimal cut-off level of 250 $\mu\text{g/g}$ and a sensitivity of 82.4% and a specificity of 87.1% compared to endoscopy. The CS FC home-test compared to endoscopy revealed an AUC of 0.89 (figure 2B), with an optimal cut-off level of 250 $\mu\text{g/g}$ and a sensitivity of 87.5% and a specificity of 67.7% compared to endoscopy. A strong correlation was found between the QOC and CS FC home-tests and FC measured by routine lab, with a Pearson's correlation coefficient of 0.75 ($P < 0.001$) and 0.89 ($p < 0.001$), respectively.

When either the MIAH or the QOC home-test was positive in CD patients, the sensitivity, specificity, PPV and NPV were 96.7%, 66.7%, 76.3% and 94.7% compared to endos-

Table 3. Test characteristics of the MIAH-CD, MIAH-UC and the combinations of the MIAH and calprotectin home-tests compared to endoscopy.

	Sensitivity (95% CI)	Specificity (95% CI)	NPV (95% CI)	PPV (95% CI)
MIAH-CD	67.6 (55.5-78.2)	81.3 (69.5-89.9)	80.0 (70.1-87.2)	69.3 (61.3-76.4)
MIAH-UC	68.2 (52.4-81.4)	80.5 (70.6-88.2)	83.3 (76.2-88.6)	63.8 (52.4-73.9)
MIAH-CD with QOC	96.7 (82.8-99.9)	66.7 (46.0-83.5)	94.7 (72.1-99.2)	76.3 (65.3-84.7)
with CS	96.2 (80.4-99.9)	58.3 (36.6-77.9)	93.3 (66.5-99.0)	71.4 (60.8-80.2)
MIAH-UC with QOC	88.2 (63.6-98.5)	71.4 (53.7-85.4)	92.6 (77.0-97.9)	60.0 (46.4-72.3)
with CS	87.5 (61.7-98.5)	63.3 (43.9-80.1)	90.5 (71.6-97.3)	56.0 (43.4-67.8)

CD, Crohn's disease; UC, ulcerative colitis; MIAH, Monitor IBD At Home questionnaire; QOC, QuantOn Cal home-test; CS, Calpro Smart home-test; NPV, negative predictive value; PPV, positive predictive value; CI, confidence interval.

copy, respectively (table 3, figure 3A, and supplementary table 3). For UC patients, when either the MIAH or the QOC home-test was positive a sensitivity of 88.2%, a specificity of 71.4%, a PPV of 60.0% and a NPV of 92.6% were obtained compared to endoscopy (table 3, figure 3B, and supplementary table 3). When the score was performed with the CS home-test, comparable results were obtained (table 3 and supplementary table 3).

Figure 1. ROC curves of the MIAH questionnaire to predict endoscopic disease activity in CD (A) and UC patients (B).

Figure 2. ROC curves of FC measured by the routine laboratory test and by the QOC and CS home-tests to predict endoscopic disease activity in CD patients (A) and in UC patients (B).

Figure 3. Value of the MIAH questionnaire, FC home-test and combination score in predicting endoscopic disease activity in CD patients (A) and in UC patients (B) with objectified endoscopic disease activity, and in CD patients (C) and in UC patients (D) without objectified endoscopic disease activity

DISCUSSION

In this study, we developed and validated the Monitor IBD At Home questionnaire, a PROM developed for monitoring of IBD disease activity in clinical practice or in tele-medicine systems. The combination of the patient-reported MIAH questionnaire and a calprotectin home-test predicted endoscopic disease activity with a sensitivity of 96.7% and NPV of 94.7% for CD patients and a sensitivity of 88.2% and NPV of 92.6% for UC patients.

Tight monitoring focusing on early recognition of mucosal inflammation and immediate treatment optimisation in case of disease activity is associated with better long-term outcome and therefore considered an emerging treatment goal for IBD patients^{4,5}. The gold standard for assessment of mucosal inflammation is endoscopy, but this is an invasive, time-consuming and costly examination and therefore not suitable nor available for routine follow-up. When compared to endoscopy, the measurement properties of the developed MIAH questionnaire alone were unsatisfactory to screen patients for active disease. Nevertheless, the questionnaire showed higher predictive values compared to endoscopy than conventional clinical disease outcomes as the HBI, CDAI and the SCCAI^{29,30} and similar results when compared to the patient-reported mHealth Index, which showed AUCs of 0.63 in patients with CD and 0.82 in patients with UC¹⁴. Other patient-reported outcomes have only been validated against conventional clinical disease outcomes and their utility to assess mucosal inflammation remains therefore unclear.

This study confirms that patient-reported questionnaires correlate moderately with endoscopic findings suggesting that disease control based on symptoms alone is not sufficient. The fact that 30% of IBD patients in clinical remission show inflammation during endoscopy and 30-50% of IBD patients have IBS-like symptoms without having mucosal inflammation during endoscopy underscores this^{31,32}. As a result, gastroenterologists frequently rely on objective biomarkers, such as C-reactive protein or FC. These biomarkers alone, however, show also insufficient accuracy to predict endoscopic disease activity and remission²⁹.

In this study, the combination of a PROM and a FC test was shown to be an excellent screening tool for endoscopic disease activity, with a sensitivity of around 90% and specificity of around 70%. The recently developed Utrecht Activity Index, which includes both symptoms and laboratory parameters, was also reliable (sensitivity 80%, specificity 92%) in predicting endoscopic disease activity in patients with CD³³. However, these laboratory parameters are not available at present for home-monitoring. The FC home-tests used in this study had similar accuracy for detecting endoscopic disease activity compared to routine lab. In contrast to routine FC assessment in the hospital laboratory, home-test results are available within 15 minutes preventing a delay in treatment initiation. In addition, the procedure is less complicated and less time-consuming for patients

as they do not have to bring their fecal sample to the hospital. A home-test, furthermore, empowers patients by more involvement in their disease management.

The main strength of this study was that we developed a PROM following the FDA recommendations, including patients' perspectives on the questions and testing of construct validity with endoscopy as golden standard. However, there are some limitations to be noted. We included a selected population of patients who had a clinical indication for endoscopy. Only a minority of patients was referred for a surveillance endoscopy or an endoscopy to confirm sustained remission in order to de-escalate therapy. As a result, a majority of included patients had symptoms, while only 40% of these patients had endoscopically active disease. This might have resulted in an overestimation of false positive MIAH questionnaires. Although we tried to minimise inter-endoscopist variability by training the endoscopists and by independently reviewing all endoscopic results, we cannot rule out any variation in test results. In addition, patient interviews were performed after the development phase, which might partially account for the differences observed between the sensitivity and specificity in the development versus validation cohort. Furthermore, the FC home-tests were performed by a researcher to minimise test variability, but also because these tests were not yet implementable for use by patients during the study period. Further studies need to focus on patients' evaluation with FC home-testing and on the best frequency of home-monitoring in order to enable tight disease control and prevent disease-related complications. Thereafter, validation studies are needed to evaluate the value of the composition of the MIAH questionnaire and a FC home-test in different patient cohorts.

In summary, we developed the MIAH questionnaire, which is the first patient-reported questionnaire to predict endoscopic inflammation in IBD patients developed according to the FDA guidelines. A combination of this questionnaire and a FC home-test shows excellent diagnostic accuracy to screen for patients who need further assessment of disease activity by clinical examination, endoscopy or imaging. This composite score is a valuable tool for tight disease control in routine clinical practice or in telemonitoring systems.

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Supplementary table 1. Correlation coefficients of the individual questions with endoscopic disease activity in Crohn's disease patients.

Questions	Response options	Correlation coefficient	P value
Stool frequency (day)	Numerical	0.513	0.000
Liquid or soft stools frequency	Numerical	0.324	0.001
Patient-reported disease activity	VAS 0-10	0.278	0.006
Urgency of defecation	No	0.236	0.020
	Yes, urgent		
	Yes, very urgent		
Mucus loss	Yes/no	0.233	0.022
Rectal bleeding	Yes/no	0.177	0.082
Stool frequency (night)	Numerical	0.173	0.089
Fatigue	VAS 0-10	0.110	0.281
Fever	Yes/no	0.092	0.369
General well-being	VAS 0-10	0.058	0.573
Perceived stress	VAS 0-10	0.053	0.604
Weight loss	Yes/no	-0.001	0.992
Abdominal pain	VAS 0-10	-0.065	0.524

Supplementary table 2. Correlation coefficients of the individual questions with endoscopic disease activity in ulcerative colitis patients.

Questions	Response options	Correlation coefficient	P value
Rectal bleeding	Yes/no	0.584	0.000
Stool frequency (day)	Numerical	0.513	0.000
Mucus loss	Yes/no	0.477	0.000
Patient-reported disease activity	VAS 0-10	0.396	0.000
General well-being	VAS 0-10	0.314	0.005
Liquid or soft stools frequency	Numerical	0.254	0.023
Urgency of defecation	No	0.226	0.044
	Yes, urgent		
	Yes, very urgent		
Weight loss	Yes/no	0.206	0.066
Stool frequency (night)	Numerical	0.176	0.117
Abdominal pain	VAS 0-10	0.157	0.165
Perceived stress	VAS 0-10	0.117	0.301
Fatigue	VAS 0-10	0.034	0.764
Fever	Yes/no	N/A	N/A

N/A= not applicable (none of the ulcerative colitis patients reported fever).

Supplementary table 3. Diagnostic accuracy of the MIAH questionnaire, the QOC home-test, the CS home-test and their combinations, compared to endoscopy.

	Mucosal inflammation (n)	Endoscopic remission (n)	Diagnostic accuracy (%)	Number of patients included (n)
MIAH-CD positive	48	12	74.1	135
MIAH-CD negative	23	52		
MIAH-UC positive	30	17	76.3	131
MIAH-UC negative	14	70		
QOC-CD positive	23	6	77.2	57
QOC-CD negative	7	21		
QOC-UC positive	14	8	78.8	52
QOC-UC negative	3	27		
CS-CD positive	20	10	68.0	50
CS-CD negative	6	14		
CS-UC positive	14	10	73.9	46
CS-UC negative	2	20		
MIAH-CD and QOC positive	12	1	82.5	57
MIAH-CD or QOC positive	17	8		
MIAH-CD and QOC negative	1	18		
MIAH-CD and CS positive	10	3	78.0	50
MIAH-CD or CS positive	15	7		
MIAH-CD and CS negative	1	14		
MIAH-UC and QOC positive	10	1	76.9	52
MIAH-UC or QOC positive	5	9		
MIAH-UC and QOC negative	2	25		
MIAH-UC and CS positive	10	1	71.7	46
MIAH-UC or CS positive	4	10		
MIAH-UC and CS negative	2	19		

CD, Crohn's disease; UC, ulcerative colitis; MIAH, Monitor IBD At Home questionnaire; QOC, QuantOn Cal home-test; CS, Calpro Smart home-test

PART II

Chapter 4

Development and feasibility study of a
telemedicine tool for all IBD patients:
myIBDcoach

Marin de Jong, Andrea van der Meulen-de Jong,
Mariëlle Romberg-Camps, Juliette Degens, Marco Becx,
Tineke Markus, Henny Tomlow, Mia Cilissen, Nienke Ipenburg,
Marthe Verwey, Laurence Colautti-Duijsens, Wim Hameeteman,
Ad Masclee, Daisy Jonkers, Marieke Pierik

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ABSTRACT

Background: Tight control of disease activity, medication side-effects and adherence are crucial to prevent disease complications and improve quality of life (QoL) in inflammatory bowel disease (IBD) patients. The chronic nature and increasing incidence of IBD demand healthcare innovations to guarantee future high quality care. Previous research proved that integrated care by telemedicine can improve outcomes of chronic diseases. Currently available IBD telemedicine tools focus on specific patient subgroups. Therefore we aimed to 1) develop a telemedicine system suitable for all IBD patients in everyday practice and 2) to test this system's feasibility.

Methods: With a structured iterative process between patients, dietitians, IBD nurse-specialists and gastroenterologists, myIBDcoach was developed. During 3 months, myIBDcoach's feasibility was tested by 30 consecutive IBD outpatients of three hospitals. Thereafter, patients and healthcare providers completed a questionnaire covering satisfaction, accessibility and experiences with myIBDcoach.

Results: MyIBDcoach enables continuous home-monitoring of IBD patients and optimises disease knowledge and communication between patients and healthcare providers. Besides disease activity, medication adherence and side-effects, myIBDcoach monitors malnutrition, smoking, QoL, fatigue, life-events, work participation, stress, anxiety and depression and provides e-learning for patient-empowerment. Patients graded the system with a mean of 7.8 out of 10 and 93% would recommend myIBDcoach to other patients.

Conclusions: We developed myIBDcoach, which enables integrated care for all IBD patients, regardless of disease severity or medication use. This feasibility study showed high satisfaction and compliance of patients and healthcare providers. To study myIBDcoach's efficacy, a multicentre randomised controlled trial has been initiated.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic disorder of the gastrointestinal tract with a peak onset in early adulthood¹. Crohn's disease (CD) and ulcerative colitis (UC) are the two main subtypes, but within these groups the clinical presentation is very heterogeneous with regard to disease location, disease behaviour, occurrence of extra-intestinal manifestations and therapy response². IBD has a significant impact on quality of life and constitutes an economic burden due to direct and indirect healthcare costs³⁻⁵.

Recent studies show that tight control of disease activity and early interventions in case of recurrence of intestinal inflammation are important to shorten flare duration and prevent complications⁶. Furthermore, most available drugs are immunosuppressives which can have severe side-effects^{7, 8}. For these reasons, continuous and personalised monitoring of IBD patients with regard to disease activity, medication use and side-effects is required. In addition, many aspects that may influence disease activity, such as stress, smoking, nutritional status and treatment adherence are not followed systematically in most IBD clinics. Interventions on these aspects may significantly improve the long-term outcome of IBD^{9, 10}. Furthermore, systematic registration of patient-reported outcome measures (PROMs) and work disability is increasingly requested by healthcare insurers to guarantee reimbursement of expensive drugs, while patients themselves also demand empowerment and more involvement with their therapy.

Continuous monitoring of this multifaceted, chronic and invasive disease, given the increasing incidence of IBD¹¹⁻¹³, will put significant pressure on gastrointestinal healthcare capacities. To guarantee personalised, high quality, efficient and affordable healthcare for IBD patients in the future, innovative solutions are warranted.

Healthcare at a distance, also known as telemedicine or eHealth, is a possible innovation that may contribute to the quality and efficiency of care for IBD patients^{12, 14, 15}. eHealth has already been implemented successfully for several other chronic diseases, such as congestive heart failure^{16, 17}, asthma¹⁸, hypertension¹⁹, chronic obstructive pulmonary disease^{20, 21} and diabetes mellitus^{22, 23}. Mounting evidence shows that direct involvement of healthcare providers, promotion of patient empowerment and integrated care improve the outcome of chronic diseases²⁴⁻²⁷.

Also for IBD patients, several telemedicine systems have been developed. Cross *et al.* developed a Home Telemanagement System for UC patients²⁸⁻³², composed of a netbook computer and an electronic weight scale that monitors symptoms, medication usage and side-effects. Elkjaer *et al.* developed a web-based system (Constant Care) to monitor disease activity and quality of life in patients with mild-to-moderate UC on 5-aminosalicylic acid (5-ASA) treatment^{26, 33}. This program was also used for individualisation of 5-ASA treatment and improvement of adherence in mild-to-moderate UC patients¹⁰ and

for individualisation of infliximab (IFX) scheduling in CD patients on IFX maintenance treatment³⁴.

Overall, these systems were shown to be feasible, safe and well-accepted by IBD patients^{35, 36}, but are developed for subgroups of IBD patients with relatively mild disease. Therefore, we aimed 1) to develop a telemedicine system for all subtypes of IBD patients in everyday clinical practice through close collaboration of patients, IBD nurse-specialists and gastroenterologists using a structured approach and 2) to test the feasibility of this system in terms of compliance and satisfaction among patients and healthcare providers.

MATERIALS AND METHODS

Development MyIBDcoach

Design and content development

Before start of the development phase, the need for an integrated eHealth system for IBD patients in the Netherlands was evaluated among different stakeholders, i.e. IBD patients from the Dutch IBD patients organization³⁷, dietitians, representatives from the pharmaceutical industry, gastroenterologists and IBD nurse-specialists from academic as well as non-academic hospitals (figure 1, phase I). Subsequently, they discussed the design of the telemonitoring program further referred to as myIBDcoach, the relevant topics and questionnaires to be included as well as safety management of home-monitoring using a structured iterative process (figure 1, phase II-V). In addition, topics for e-learning modules were selected and subsequently developed by topic-specific experts and reviewed by an independent gastroenterologist (figure 1, phase VI).

To facilitate broad support and implementation of myIBDcoach and to improve co-operation between the various stakeholders, a foundation was instituted³⁸. The director of the Dutch IBD patient organisation, two gastroenterologists, an accountant and an assistant professor health analytics systems constitute the board. Representatives of the aforementioned stakeholders, as well as of the IBD section of the NVGE (Dutch Association for Gastroenterology), the NVMDL (Dutch Association for Gastroenterologists) and the N-NIC (association of IBD nurse-specialists) form a separate committee which decides on the design and content of myIBDcoach.

Technological development

The technological development of myIBDcoach was conducted by Sananet BV³⁹, specialised in development and implementation of telemedicine and self-management

tools. They integrated relevant information and questionnaires into both a web-based and an HTML application and created a secure link between patients and the hospital.

The system includes so-called monitoring modules, intensified monitoring modules, outpatient visit modules, e-learning modules, a follow-up plan and an administrator page used by the healthcare provider (figure 2). The modules will be discussed in detail later. MyIBDcoach meets all legal requirements in line with the European laws regarding security and confidentiality of patient data.

Feasibility study myIBDcoach

After the technological and content development, a feasibility study was planned in three clinical centres to evaluate compliance, satisfaction, accessibility and experiences with myIBDcoach from both healthcare providers and patients.

From November 2012 until March 2013, 30 patients were recruited from the tertiary referral centres Maastricht University Medical Centre+ and Leiden University Medical Centre, and from the non-academic hospital Zuyderland Medical Centre. Patients between 18 and 75 years of age, fulfilling the international diagnostic criteria for IBD⁴⁰, were eligible for inclusion. Exclusion criteria consisted of inability to read or understand the informed consent form, lack of internet access by computer, tablet or smartphone or a hospital admission due to IBD disease activity within two weeks prior to inclusion because of practical reasons.

Participating patients followed a short practical training on how to use myIBDcoach. Following this, participants received a unique username and password and were asked to log on to <http://www.mijnibdcoach.nl>. During a 3-month study period, patients were requested to complete the myIBDcoach monitoring module monthly. At the end of the study period, patients and healthcare providers from the participating hospitals were asked to fill out an evaluation questionnaire regarding satisfaction, accessibility and experiences with myIBDcoach.

Ethical considerations

The study was approved by the Medical Research Ethics Committee of the Maastricht University Medical Centre (METC azM/UM), which waived the requirement to obtain informed consent. The study protocol conformed to the provisions of the declaration of Helsinki.

Data collection and outcome measures

Feasibility data in terms of satisfaction, accessibility and experiences with myIBDcoach were collected from patients' and healthcare providers' evaluation questionnaires. Compliance with myIBDcoach in this pilot study was predefined as $\geq 70\%$ adherence with the monthly monitoring modules. Demographic information was obtained from all patients at the time of recruitment.

Statistical analyses

Descriptive analyses to evaluate demographic information and to assess feasibility with myIBDcoach were performed using IBM SPSS statistics 22.0.

RESULTS

Development MyIBDcoach

Technological development

A personal web-based telemedicine system for IBD patients, myIBDcoach, was designed and developed as a secure webpage (<http://www.mijnibdcoach.nl>) and HTML application on a tablet or smartphone (figure 3). MyIBDcoach can be used as a stand-alone programme, however, incorporation in different hospital electronic patient files is technically also possible. Sananet BV provides technical support for all participants (patients and healthcare providers).

Content development

During the first brainstorm meeting with the identified stakeholders (figure 1, phase II), patients emphasised the importance of better communication with the hospital, tailored information about their disease and medication, as well as patient-centred care. Gastroenterologists noticed that a more holistic approach to the IBD-patient was needed, since many disease-related aspects, including nutrition, work productivity, smoking, anxiety and depression were often not addressed in current practice, but are of relevance for disease outcome and health-related quality of life. Furthermore the importance to monitor disease activity and side-effects of (immunosuppressive) drugs was emphasised. Both gastroenterologists and the representatives from the pharmaceutical industry indicated better monitoring of therapy adherence to be of relevance to optimise treatment. At home monitoring of disease activity and disease-related aspects at regular intervals requires validated patient-reported outcome measures (PROMs), which are also demanded by governments for registration of efficacy endpoints for expensive drugs.

Based on literature review, validated PROMs on medication adherence, medication satisfaction, nutritional status, quality of life, work productivity, anxiety and depression, social support and fatigue, were selected. When different validated questionnaires on the same topic were available in the literature, the shortest applicable questionnaire was chosen if there were no major advantages of the other questionnaires, to constrain monitoring modules to a reasonable length.

Figure 1. Different phases of design and content development of myIBDcoach

Validated PROMs for disease activity and infectious events were not available in the literature (figure 1, phase III). Existing-patient reported disease activity questionnaires, such as the Patient Harvey Bradshaw Index and the Patient Simple Clinical Colitis Activity Index, are not validated against endoscopy and show poor correlation with endoscopic disease activity⁴¹⁻⁴⁴. Therefore, myIBDcoach utilises a newly developed Monitor IBD At Home questionnaire (MIAH)⁴⁵ (figure 1, phase IV). This is a symptom-based patient-reported outcome measure that is validated against endoscopy and does not require laboratory tests or physical examination. The MIAH shows good diagnostic accuracy to screen for patients who need further assessment of disease activity with biochemical markers, imaging or endoscopy⁴⁵, and excellent accuracy when combined with a fecal calprotectin home-test⁴⁶. A score of ≤ 3.6 is defined as remission. In addition, a new questionnaire on medication side-effects and infectious events was developed.

A schematic overview of the design of myIBDcoach is shown in figure 2 and an overview of questionnaires as well as their frequency of monitoring is given in table 1.

Monitoring module

Patients are requested to complete the regular 'monitoring module' monthly, which contains questions regarding disease activity (MIAH)⁴⁵, extra-intestinal manifestations, medication use, medication adherence (Morisky Medication Adherence Scale (MMAS-8)(47)), medication satisfaction (Treatment Satisfaction Questionnaire for Medication (TSQM)(48)) and medication side-effects including infections. In addition, the monitoring module measures general disease aspects as quality of life (EuroQol instrument (EQ-5D)(49) and Short Form Health Survey (SF-12)(50)), work productivity (Work Productivity and Activity Impairment (WPAI)(51)), nutritional status (Malnutrition Screening Tool (MST)(52)) and Short Nutritional Assessment Questionnaire (SNAQ)(53)), fatigue, physical exercise, stress, life-events, anxiety and depression, social support and self-management skills. When the disease is in remission, defined as three consecutive MIAH-scores ≤ 3.6 , patients will be asked if they prefer to fill out the questionnaire once per three months. In case of a flare, defined as a MIAH-score > 3.6 , patients are requested to log on weekly and complete the 'intensified monitoring module' on disease activity and medication use until the symptoms subside.

Back-office

The administrator page, further referred to as back-office, is used by the patient's own healthcare provider, i.e. a gastroenterologist and/or an IBD nurse (specialist), and provides an overview of all participating patients per centre. As myIBDcoach is a self-management system, patients are in the lead to contact the healthcare provider in case of symptoms or other questions. To ensure safety of home-monitoring, alerts (red flags) are created in the back-office when values recorded from the questions of the monitor-

ing module exceed pre-defined thresholds. In case of an alert, the healthcare provider will contact the patient for further evaluation. Based on the extent and severity of the complaints they decide whether the patient should be seen at the outpatient clinic. At any time, patients can communicate easily with their healthcare provider by sending a message through the secure connection to the back-office of the healthcare provider. Every new message creates an alert in the back-office.

Outpatient visit module

When a routine outpatient visit is scheduled, patients are asked to prepare this visit by completing the 'outpatient visit module', which registers patient-reported disease activity (MIAH)⁴⁵, extra-intestinal manifestations⁵⁴ and parameters which may influence long-term disease outcomes such as quality of life (Short Inflammatory Bowel Disease Questionnaire (SIBDQ)⁵⁵, smoking, work productivity (WPAI)⁵¹, intimacy and sexuality, anxiety and depression (Hospital Anxiety and Depression Scale (HADS)⁵⁶), medication adherence, social support (Social Support List (SSL)⁵⁷) and fatigue (Shortened fatigue questionnaire (SFQ)⁵⁸). The values recorded from these questionnaires are presented in a clear overview to make the consultation with the gastroenterologist as efficient as possible and to make sure all relevant topics will be discussed and patients will be referred to other specialists when necessary. Furthermore, patients are given the opportunity to note what they would like to discuss with their healthcare provider during the visit.

Figure 2. Schematic overview of different functions of myIBDcoach: monitoring, personal follow-up plan, e-learning modules and communication. An overview of content and frequency of modules is shown in table 1. When values recorded from the questions of the monitoring modules exceed pre-defined thresholds, alerts (red flags) are created in the back-office.

E-learning modules

To improve patients' knowledge on IBD we developed patient-tailored interactive e-learning modules about CD and UC in general, 5-ASA, immunosuppressives or anti-tumor necrosis factor therapy, medication adherence, smoking cessation, (mal)nutrition,

how to prevent or reduce symptoms (self-management), fatigue, work productivity, pregnancy, intimacy, anxiety and depression, influenza vaccination and about how to receive adequate support from friends, family and colleagues (figure 1, phase VI). Both patients and healthcare providers can start an e-learning module, i.e. patients can be advised to perform a certain e-learning module whenever their healthcare provider considers it desirable or when the patients themselves are interested in a specific topic.

Self-management

All information derived from the monitoring and outpatient visit modules is presented in a personal follow-up plan. The follow-up plan summarises all disease aspects in tables and graphs for both the patient and the healthcare provider (figure 4). By providing insight in their follow-up plan, we aim to improve patients' self-management and stimulate patient-empowerment.

Figure 3. MyIBDcoach

Client
Visits
Follow-up plan
E-learning modules
Messages

Monitoring
Monitoring module: Monthly
Intensified monitoring module: Disabled
Change

Search visit 8-2-2016

Monitoring module
Disease activity 8-2-2016
Disease activity IBD

Infection surveillance 8-2-2016
☒ Patient had an infection or fever: No
☒ Patient had fever more than 38.5 degrees Celsius: No

Measurements 8-2-2016
☒ Weight: 163 cm Weight: 55 kg BMI: 20.7 normal weight

Domains 8-2-2016

General wellbeing	Very bad Very good
Treatment satisfaction	Good Not
Medication adherence	Always Never
Fatigue	Rarely Always
Nutritional status	Adequate Inadequate
Depression	Rarely Always
Anxiety	Rarely Always
Embarrassment	Rarely Always
Social support	A lot None
Support employer	A lot None
Physical activity	Daily Hardly
Stress	None A lot
Exacerbation management	Exactly Not exact
Life-events	☒ Divorce

Figure 4. Follow-up plan of myIBDcoach.

Results feasibility study myIBDcoach

MyIBDcoach was pilot-tested by 30 IBD patients and 8 healthcare providers. Patient characteristics are shown in table 2. Compliance with the monthly monitoring modules was 100%. Patients judged myIBDcoach with a mean score of 7.8 out of 10, and healthcare providers gave a mean score of 8.0 out of 10. Both patients and healthcare providers found the design and accessibility of the system of high quality. One patient thought the system was time-consuming. Ninety-three percent of the patients would recommend myIBDcoach to other patients.

During the 3-month study period, 40% of the patients (n=12) contacted their healthcare provider through myIBDcoach for urgent symptoms or general questions. Of these patients, 83% percent found that this contact had a positive contribution to the overall contact with their healthcare provider. Ninety percent of the patients completed at least one e-learning module. After completing the e-learning modules, a majority of these patients felt that their general knowledge about their disease had improved.

Table 1. Design of myIBDcoach

Section	Function	Frequency
Monitoring module	1. Monitors patient-reported disease activity (MIAH (45)), extra-intestinal manifestations, medication use, adherence (MMAS-8 (47)), satisfaction (TSQM (48)) and side-effects 2. Monitors general disease aspects: nutritional status (MST (52) and SNAQ (53)), quality of life (EQ-5D (49), SF-12 (50)), work productivity (WPAI (51)), infections and single questions on fatigue, physical exercise, stress, life-events, anxiety and depression, social support and self-management skills.	Monthly or every 3 months when sustained remission
Intensified monitoring module	Monitors patient-reported disease activity (MIAH (45)) and medication usage in case of a flare.	Weekly
Outpatient visit module	Registers patient-reported disease activity (MIAH (45)), extra-intestinal manifestations, quality of life (SIBDQ (55)), smoking, work productivity (WPAI (51)), intimacy and sexuality, anxiety and depression (HADS (56)), medication adherence, nutritional status (MST (52) and SNAQ (53)), social support (SSL (57)) and fatigue (SFQ (58)) and a topic patients would like discuss with their healthcare provider during the upcoming outpatient visit.	Yearly/when applicable
E-learning module	Offers patient tailored information on 16 selected topics.	When applicable
Communication	Facilitates communication between patient and healthcare provider and provides systematic documentation of communication.	24/7 available
Follow-up plan	Gives a clear overview of follow-up for both patient and healthcare provider.	24/7 available

MIAH, Monitor IBD At Home; MMAS-8, Morisky Medication Adherence Scale; TSQM, Treatment Satisfaction Questionnaire for Medication; MST, Malnutrition Screening Tool; SNAQ, Short Nutritional Assessment Questionnaire; EQ-5D, EuroQol instrument; SF-12, Short Form Health Survey; WPAI, Work Productivity and Activity Impairment; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; HADS, Hospital Anxiety and Depression Scale; SSL, Social Support List; SFQ, Shortened Fatigue Questionnaire.

Table 2. Baseline characteristics of the participating patients in the feasibility study

	Participating patients (n=30)
Age, mean (SD)	44.2 (11.7)
Gender, N (%)	
Male	12 (40.0)
Disease duration (years), mean (SD)	14.7 (13.8)
Phenotype, N (%)	
CD	17 (56.7)
UC	13 (43.3)

Table 3. Overview previously developed and tested telemedicine tools in IBD

	Application	Study population	Study design	Assessments/education	Frequency measurements	Outcomes
Cross et al. (IBD 2012)	UC-HAT: computer with electronic weight scale, decision support server and web-based clinician portal	47 UC patients	Randomised controlled trial	Symptoms, medication usage, adherence and side-effects	Weekly	UC-HAT shows high acceptance and adherence to self-testing. No differences in disease activity, medication adherence and quality of life between groups.
Pedersen et al. (AP&T 2012)	Constant-Care: web-based IFX treatment approach for CD patients	27 CD patients with IFX maintenance therapy	Controlled trial	Disease specific education Disease activity and fecal calprotectin	Weekly	Patients are able to self-manage with IFX using the web guided maintenance therapy. No statistically significant differences in the mean interval between IFX infusions between groups were seen.
Elkjaer et al. (Gut 2013)	Constant-Care: web-based telemonitoring	333 mild-moderate UC patients with 5-ASA therapy	Randomised controlled trial	Disease activity, medication usage and quality of life E-learning	Remission: monthly Relapse: daily	Constant care is feasible, safe and cost-effective. Improvement of treatment adherence, IBD knowledge, quality of life and shorter relapse duration in intervention group.
Pedersen et al. (IBD 2014)	Constant-Care: web-based guided 5-ASA dose regulation	95 mild-moderate UC patients with maintenance systemic and/or topical 5-ASA therapy	Prospective open-label study	Disease activity and fecal calprotectin	Weekly	Feasible and safe. Web-guided 5-ASA therapy leads to improvement of therapy adherence.

5-ASA, 5-aminosalicylic acid; IFX, infliximab

DISCUSSION

This paper describes the systematic development of the first telemedicine system that enables home-monitoring for all subtypes of IBD patients. A pilot study proved that myIBDcoach is feasible for use in routine care and well-accepted by patients and healthcare providers. Patients were compliant with the programme, indicated that myIBDcoach facilitated communication with their healthcare providers and that the e-learning modules improved their knowledge about IBD.

During this pilot study, adherence to the system was very high. In the literature telemedicine tools faced attrition rates as high as 14-44% over time^{10, 15, 26, 30, 34}. We aimed to increase compliance with myIBDcoach by involving patients in all stages of the development, by providing feedback to the patient in a follow-up plan and by constraining questionnaires to a reasonable length with individualised frequency. To increase patient empowerment, myIBDcoach contains e-learning modules, promotes patients' self-management and facilitates communication between patients and healthcare providers. The finding that 93% of patients would recommend myIBDcoach to other patients reflects a high patient satisfaction rate. Additionally, to enhance user friendliness, myIBDcoach can also be used on a smartphone or tablet.

Despite proven benefits of telemedicine for IBD and other chronic diseases, few systems are implemented in every day care. One possible reason might be that previously published tools monitor, educate or empower specific groups of patients^{10, 26, 30, 34} (table 3). Contrary to this, we deliberately designed myIBDcoach for all subtypes of IBD patients in different settings, regardless of phenotype, disease activity or medication use. In addition, we wanted myIBDcoach to focus on all facets of this complex disease, i.e. not only directly IBD-related aspects, but also on stress, smoking, nutritional status and treatment adherence, which may impact disease outcome and quality of life. Prevention of treatment non-adherence for example, reported to be as high as 40-60% in IBD patients, has a significant impact on the risk of disease relapse, hospitalisation, healthcare costs and work absenteeism^{9, 10}.

Jackson et al. recently reviewed the entire spectrum of eHealth interventions used for IBD management and provided recommendations for the design of future IBD eHealth technologies to facilitate implementation¹⁵. They emphasised the importance of a framework for development, evaluation and implementation of eHealth interventions and the relevance of patient and clinician involvement in all stages. MyIBDcoach was developed through close collaboration between patients, nurses and gastroenterologists during all phases of the development. The rights for the content of the system are governed by a nonprofit foundation. The board and content committee of the myIBDcoach foundation consist of patients and clinicians from all important Dutch stakeholders involved

in IBD care. The foundation carefully monitored all phases of the developmental and implementation process.

Since the pilot study showed that IBD care with myIBDcoach is feasible and can be used for routine follow-up, we initiated a randomised controlled trial to investigate whether the integrated and holistic approach of myIBDcoach is safe and increases efficiency of IBD care compared to standard care. A total of 909 consecutive IBD outpatients from academic and non-academic hospitals, regardless of disease severity and activity and treatment strategies ranging from no treatment to combined immunosuppressives, were included and randomised to care via myIBDcoach or standard care for one year. The primary endpoints are the number of outpatient visits and patient-reported quality of IBD healthcare. Secondary endpoints include disease outcomes (i.e. flares, corticosteroid use, hospitalisations, emergency visits and IBD-related surgery), medication adherence and quality of life. We will also assess whether use of myIBDcoach leads to patient empowerment by an increase in knowledge about the disease and treatment and whether myIBDcoach is a suitable tool for structured collection of PROMs.

In conclusion, we developed myIBDcoach, which enables integrated and holistic care for all IBD patients in both academic and non-academic centres. This feasibility study showed high satisfaction of patients and healthcare providers with the system. Following these positive results, a large multicentre randomised controlled trial has been initiated.

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Chapter 5

Telemedicine for management of inflammatory bowel disease (myIBDcoach): a pragmatic, multicentre, randomised controlled trial

Marin de Jong, Andrea van der Meulen-de Jong,
Mariëlle Romberg-Camps, Marco Becx, Jeroen Maljaars,
Mia Cilissen, Ad van Bodegraven, Nofel Mahmmod, Tineke Markus,
Wim Hameeteman, Gerard Dijkstra, Ad Masclee, Annelies Boonen,
Bjorn Winkens, Astrid van Tubergen, Daisy Jonkers, Marieke Pierik

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ABSTRACT

Background Tight and personalised control of inflammatory bowel disease in a traditional setting is challenging because of the disease complexity, high pressure on outpatient clinics, and rising incidence. We compared the effects of self-management with a telemedicine system, which was developed for all subtypes of inflammatory bowel disease, on healthcare utilisation and patient-reported quality of care versus standard care.

Methods We did this pragmatic, randomised trial in two academic and two non-academic hospitals in the Netherlands. Outpatients aged 18–75 years with inflammatory bowel disease and without an ileoanal or ileorectal pouch anastomosis, who had internet access and Dutch proficiency, were randomly assigned (1:1) to care via a telemedicine system (myIBDcoach) that monitors and registers disease activity or standard care and followed up for 12 months. Randomisation was done with a computer-generated sequence and used the minimisation method. Participants, healthcare providers, and staff who assessed outcome measures were not masked to treatment allocation. Primary outcomes were the number of outpatient visits and patient-reported quality of care (assessed by visual analogue scale score 0–10). Safety endpoints were the numbers of flares, corticosteroid courses, hospital admissions, emergency visits, and surgeries. Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT02173002.

Findings Between Sept 9, 2014, and May 18, 2015, 909 patients were randomly assigned to telemedicine (n=465) or standard care (n=444). At 12 months, the mean number of outpatient visits to the gastroenterologist or nurse was significantly lower in the telemedicine group (1.55 [SD 1.50]) than in the standard care group (2.34 [1.64]; difference –0.79 [95% CI –0.98 to –0.59]; $p<0.0001$), as was the mean number of hospital admissions (0.05 [0.28] vs 0.10 [0.43]; difference –0.05 [–0.10 to 0.00]; $p=0.046$). At 12 months, both groups reported high mean patient-reported quality of care scores (8.16 [1.37] in the telemedicine group vs 8.27 [1.28] in the standard care group; difference 0.10 [–0.13 to 0.32]; $p=0.411$). The mean numbers of flares, corticosteroid courses, emergency visits, and surgeries did not differ between groups.

Interpretation Telemedicine was safe and reduced outpatient visits and hospital admissions compared with standard care. This self-management tool might be useful for reorganising care of inflammatory bowel disease towards personalised and value-based healthcare.

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed and MEDLINE for randomised controlled trials of telemedicine in inflammatory bowel diseases published up to Dec 20, 2016, with the terms “telemedicine”, “eHealth”, “mHealth”, “inflammatory bowel disease”, “randomised controlled trial”, and “adults”. This search retrieved two randomised studies, both of which were in patients with ulcerative colitis. The first trial compared self-testing of disease activity and weight measurements versus standard care in 47 patients; no differences were seen between groups in disease activity, medication adherence, and quality of life. The second trial included 333 patients with mild-to-moderate disease treated with mesalazine and found that tight disease monitoring and personalised treatment strategies resulted in an improvement of patient empowerment, quality of life, and medication adherence, and a reduction in outpatient visits and relapse duration compared with usual care. Because both studies reported data on the effects of telemedicine for a specific subgroup, no reliable conclusion could be drawn on the effectiveness of telemedicine for the entire population of patients with inflammatory bowel disease or on which subtypes of patients are likely to benefit most. This shortcoming compromises the use of telemedicine systems in real-world settings.

Added value of this study

Our study includes data on the effects of telemedicine in patients with all subtypes of inflammatory bowel disease, irrespective of phenotype, disease course, or medication use. Telemonitoring in combination with patient-tailored information, a personal care plan, easy, accessible contact with the inflammatory bowel disease nurse, and registration of patient-reported outcome measures resulted in a reduction in healthcare utilisation and hospital admissions. Furthermore, the telemedicine system myIBDcoach improved medication adherence and patients reported similar scores for quality of care compared with the standard care group. These results were consistent across different patient subtypes. Our findings accord with those in other chronic relapsing-remitting diseases and suggest that tight disease monitoring and early intervention in case of a relapse can prevent admission to hospital. Trials with a longer follow-up period are required to determine whether telemedicine can change the natural disease course of chronic diseases in the long-term.

Implications of all the available evidence

Routine follow-up of patients with inflammatory bowel disease, traditionally consisting of prescheduled visits that are unlikely to correspond with its unpredictable clinical course, puts increasing pressure on outpatient clinics, compromising accessibility and quality of care. Implementation of telemedicine in inflammatory bowel disease care bridges the gap between the healthcare workers' requests for tight disease monitoring and continuity of care in an overburdened outpatient setting and patients' demands for more involvement in disease management. Telemedicine is safe, highly accepted by patients and healthcare workers, and can be used to reorganise care for patients with all subtypes of inflammatory bowel disease. In our clinic, myIBDcoach will be used in a value-based healthcare initiative. Furthermore, patients in remission or with mild disease will be monitored and guided with telemedicine supervised by a specialised nurse to guarantee adequate access to the gastroenterologists' outpatient clinic for those patients with complex disease or in need of urgent action.

INTRODUCTION

Inflammatory bowel disease is a group of chronic, relapsing inflammatory disorders of the gut, with Crohn's disease and ulcerative colitis being the main subtypes. The clinical presentations of these diseases vary widely among individuals, as shown by variations in disease location and behaviour, relapse frequency, extra-intestinal manifestations, complications, and responses to treatment.¹

Traditionally, management of inflammatory bowel disease consists of standard scheduled follow-up visits, with a frequency based on medical treatment, but independent of the occurrence of unpredictable flares.^{2,3} Until recently, the primary treatment goal was induction and maintenance of clinical remission. However, disease management based on treating symptoms alone did not improve long-term outcomes, defined as the numbers of flares, courses of corticosteroid treatment, hospital admissions, complications, and surgeries.^{4,5} Therefore, recent guidelines advocate more stringent management, involving tight control of disease activity and early intervention in patients with intestinal inflammation.⁶ Other interventions address aspects of inflammatory bowel disease that might influence disease activity, such as non-adherence to treatment, unfavourable nutritional status, smoking, and psychological factors.⁷⁻⁹ These interventions were shown to reduce the rates of disease relapse, healthcare utilisation including hospital admission, and absence from work in subsets of patients.⁷⁻⁹ This approach, however, has not been systematically implemented in routine care, because acquiring all the necessary information at the right moment for every individual patient remains a challenge.

Furthermore, the heterogeneous nature of inflammatory bowel disease, combined with an absence of adequate markers for patient stratification, can lead to the underuse or overuse of resources.

Tight control of disease activity and personalised monitoring of all relevant health parameters during traditional visits put substantial pressure on patients' time and the capacity of outpatient clinics. The incidence of inflammatory bowel disease is increasing and insurance companies, governments, and patient organisations increasingly demand registration of patient-reported outcome measures, patient-reported experience measures, and quality metrics.^{10–13} Therefore, reorganisation of healthcare for patients with inflammatory bowel disease is warranted.

Telemedicine systems, which have been used to manage chronic diseases, such as congestive heart failure and chronic obstructive pulmonary disease, have been shown to improve quality of care and could help optimise the use of available resources.^{14,15} Telemedicine allows for the strict and instantaneous follow-up of health parameters and timely, personalised interventions. Moreover, these systems can provide tailored information based on each patient's needs.

At present, few telemedicine systems that can improve disease outcomes, increase patients' empowerment, and reduce healthcare utilisation are available for patients with inflammatory bowel disease.^{7,16–21} However, these tools were developed for patients with specific subtypes of inflammatory bowel disease, consisting of those with mild-to-moderate disease activity. Studies provide inconsistent results on the effects of these telemedicine systems on disease outcomes, compromising their use in real-world settings.

We therefore developed a telemedicine system (myIBDcoach) that monitors and registers disease activity in patients with all subtypes of inflammatory bowel disease. This system, which can be used in both academic and non-academic hospitals, also monitors other disease-related parameters, including patient-reported outcome measures and quality metrics. This information is displayed in a manner understood by the user and his or her healthcare providers. Integrated care and patient empowerment are promoted by a communication function and a wide range of web-based learning methods. A pilot study showed that integration of myIBDcoach into routine care was feasible and well accepted by patients as well as healthcare providers.²² We postulated that use of this telemedicine system in routine care could reduce healthcare utilisation, while ensuring tight disease monitoring and high patient-experienced quality of care. We did a pragmatic, multicentre, randomised controlled trial to investigate the effect of care with this telemedicine system on outpatient visits, patient-reported quality of care, and disease outcomes, and compared these effects with those of standard care.

METHODS

Study design and participants

This pragmatic randomised trial was done at four hospitals in the Netherlands: two academic hospitals (Maastricht University Medical Centre and Leiden University Medical Centre), and two large, non-academic, regional hospitals (Zuyderland Medical Centre, Sittard, and St Antonius Hospital, Nieuwegein). Each participating hospital serves 1500–2000 patients with inflammatory bowel disease, had one or two dedicated nurses or nurse specialists, and had an e-mail and telephone consultation structure for patients with inflammatory bowel disease to contact the hospital. Furthermore, each hospital provided patients with the opportunity to consult by telephone with a nurse (at least) three times per week at fixed timepoints. Patients were enrolled at the outpatient clinic of the four participating hospitals. All consecutive patients between 18 and 75 years of age, fulfilling the international diagnostic criteria for inflammatory bowel disease,²³ were eligible for inclusion. Exclusion criteria were an inability to read or understand the informed consent form, and lack of internet access by computer, tablet, or smartphone. Additionally, patients with a hospital admission within 2 weeks before inclusion were excluded for ethical reasons, because these patients were deemed unable to make an informed decision for participation. Patients with an ileoanal pouch or ileorectal anastomosis were also excluded. The study was approved by the medical research ethics committee of the Maastricht University Medical Centre. This approval was applicable to all participating centres. The study protocol is available online in Dutch.

Randomisation and masking

After signing the informed consent form, patients were randomly assigned (1:1) to care via the telemedicine system (intervention) or standard care (control). Randomisation was done with ALEA Screening and Enrolment Application Software using the minimisation method, stratified for medical centre, subtypes of inflammatory bowel disease (Crohn's disease or ulcerative colitis), and treatment (no medication or mesalazine; immunosuppressive drugs; or biological therapy). Participants, healthcare providers, and staff who assessed outcome measures were not masked to treatment allocation.

Procedures

The details of the telemedicine system myIBDcoach have been described elsewhere.²² MyIBDcoach is a secured webpage with an HTML application for tablet or smartphone (figure 1). The system includes monthly monitoring modules, which contain questions regarding disease activity, medication use, treatment adherence, treatment satisfaction, and side-effects, including infections. The system also includes questions on factors affecting disease (including nutritional status, smoking, stress, life events, anxiety and

depression, social support, physical exercise, and self-management skills), and patient-reported outcome measures on quality of life and work productivity. In monitoring disease activity, myIBDcoach uses the newly developed Monitor IBD At Home (MIAH) questionnaire, a symptom-based patient-reported outcome measure validated relative to endoscopy. This questionnaire does not require laboratory tests or physical examination, and shows good diagnostic accuracy in screening for patients requiring further assessment of disease activity with biochemical markers, imaging, or endoscopy.²⁴ When the disease was in remission, defined as three consecutive low monthly MIAH scores, patients were allowed to complete the monitoring module once every 3 months. Furthermore, the system includes intensified monitoring modules (weekly in case of flare), outpatient visit modules (to prepare for an outpatient visit), e-learning modules, a personal care plan, and an administrator page used by the healthcare provider (ie, gastroenterologist or nurse). When parameters recorded by the monitoring modules exceeded predefined thresholds, the safety and continuity of care were ensured by the creation of alerts (red flags) on the administrator page of each local hospital. In all participating centres, the administrator page was checked at least twice daily apart from weekend

Figure 1. Overview of the elements of the telemedicine tool myIBDcoach: 1) Modules containing different questionnaires: standard monitoring (every month, or every 3 months when the disease is in remission), intensified monitoring (weekly in case of a flare) and outpatient visit monitoring (to prepare an outpatient visit). 2) Personal care plan: summary and visualisation of health parameters, PROMs and quality metrics. 3) e-learning modules: interactive patient-tailored information on topics such as medications, adherence to medication, smoking cessation, (mal)nutrition, methods to prevent or reduce symptoms (self-management), fatigue, work productivity, anxiety and depression. 4) Communication: secure message connection between patient and healthcare providers' back-office.

days. If an alert was received, a healthcare provider on the local team contacted the patient for further assessment within two working days. Visits to the outpatient clinic were based on the nature and severity of the clinical complaints. At any time, patients were able to communicate easily with their healthcare provider by sending a message to the healthcare providers' administration office.

Patients assigned to the intervention group received instructions, a username, and a password for the telemedicine system. Participants used the system for 12 months and were instructed to plan at least one routine outpatient visit per year. Additional follow-up visits were scheduled on the basis of alarm symptoms recognised by the telemedicine system or at the requests of individual patients. Patients in the standard care group continued their routine follow-up visits following the local protocol, with an opportunity to schedule an extra visit if symptoms relapsed. At baseline and after 12 months, all participants received a paper questionnaire regarding perceived quality of care, medication adherence, quality of life, self-efficacy, disease-related and medication-related knowledge, and smoking behaviour.

Outcomes

The primary outcomes were the number of outpatient visits and patient-reported quality of care. The number of outpatient visits and telephone consultations with gastroenterologists and nurses during the 12 month period were retrieved from patients' electronic medical records. Because validated patient-reported quality of care questionnaires have insufficient content validity for telemedicine interventions, patient-reported quality of care was measured with seven relevant domains derived from different questionnaires. These domains included visual analogue scale (VAS) scores (0–10; higher score indicates higher quality) on patient satisfaction with healthcare, patients' experiences contacting their healthcare providers, and the extent to which healthcare meets patients' expectations. Questions were also included on the healthcare workers' timeliness of response to questions and symptoms, healthcare workers' fulfilment of agreements and attentiveness to acute situations, and hospital accessibility in case of symptoms. A mean score of 8 out of 10 or higher was predefined as perceived high quality.

Secondary outcomes were adherence to treatment, quality of life, self-efficacy, disease-related and medication-related knowledge, smoking behaviour, and disease outcomes. Disease outcomes were the numbers of flares and inflammatory bowel disease-related hospital admissions, emergency visits, surgeries, and corticosteroid use during the 12 months of follow-up. Flares were defined as clinical symptoms indicative of disease activity with, as a rule, concomitant calprotectin of more than 250 µg/g in the stool or active disease determined by endoscopy, MRI, or CT. In daily practice, in case of clinically severe symptoms suggestive for disease activity, the treating physician occasionally judged these symptoms to be evident enough to adjust therapy. Therefore, to

capture all clinical flares, clinical episodes were defined as flares if symptoms suggestive of disease activity resulted in a dose escalation or initiation of a new drug to induce remission. Medication adherence was measured with the eight-item Morisky Medication Adherence Scale,²⁵ with scores below 6 defined as low adherence, scores between 6 and 8 defined as moderate adherence, and a score of 8 defined as high adherence. Quality of life was measured with the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), a ten-item questionnaire that covers four domains: bowel symptoms, systemic symptoms, emotional health, and social functions.²⁶ Overall scores on the SIBDQ range from 10 to 70, with a lower score indicating lower quality of life. Self-efficacy, defined as the perception of one's ability to engage in skills required to master a new challenge despite obstacles, was measured with the 29-item inflammatory bowel disease self-efficacy scale (IBD-SES).²⁷ Questions are grouped into four domains: managing stress and emotions, managing medical care, managing symptoms and disease, and maintaining remission. Overall scores on the IBD-SES range from 29 to 290, with higher scores indicating higher self-efficacy and thus better self-management and greater patient empowerment. Knowledge of inflammatory bowel disease and medication were both assessed by a VAS score (0–10; higher score indicates better knowledge), whereas smoking behaviour was assessed with a categorical question (non-smoker, active-smoker, or ex-smoker).

Statistical analysis

A sample size of 435 patients per group was estimated as sufficient to detect a difference of one outpatient visit per year (SD 2.4) and 0.5 difference in mean quality of care on a VAS scale (SD 1.4), with 80% power, a 5% significance level, and assuming a 10% dropout rate. Data were analysed on an intention-to-treat basis. Between-group differences in the number of outpatient consultations and disease outcomes were analysed by multivariable linear regression adjusted for the stratification criteria (medical centre [four centres], subtypes of inflammatory bowel disease [Crohn's disease or ulcerative colitis], and treatment [no medication or mesalazine; immunosuppressive drugs; or biological therapy]) and for age (numerical), sex (male or female), disease duration (numerical), disease activity at baseline (remission or active), smoking (non-smoker, active-smoker, or ex-smoker), and educational level (five levels). Because the normality assumption might be violated because of outliers, its effect on the results was checked by comparing the obtained confidence intervals with those after bootstrapping. The multiple imputation method was used for missing outcomes and covariates, in which 20 complete datasets were created using all other variables in the aforementioned analysis model (outcome and covariate, including study group) to impute the missing data. Linear mixed model analyses were used to assess differences in patient-reported outcomes at baseline and 12 months; outcomes analysed included quality of care, quality of life, medication adherence, self-efficacy, and disease-related and medication-related knowledge.

An unstructured covariance structure for the two repeated measures was considered and a likelihood based approach was used for missing outcome variables. Results were corrected for stratification criteria and for age, sex, disease duration, disease activity at baseline, smoking, and educational level. The consistency of the intervention effect was assessed across subtypes of sex, age (18–30, 31–50, and >50 years), subtypes of inflammatory bowel disease (Crohn's disease and ulcerative colitis), setting (academic and non-academic), medication (no medication or mesalazine; immunosuppressive drugs; and biological therapy), and disease duration (0–5, 6–10, and >10 years), by post-hoc analyses where interaction terms of these variables with group (intervention and control) were added separately to the aforementioned linear regression and linear mixed models. The adjusted intervention effects that were estimated with these models are reported together with their 95% CI and p values. Logistic regression analysis was used to assess the intervention effect on smoking behaviour (active vs non-active [ex-smoker or non-smoker]) and was corrected for baseline smoking behaviour (active vs non-active) and educational level. A two-sided $p \leq 0.05$ was defined as statistically significant. All statistical analyses were done with SPSS version 22.0. This trial is registered with ClinicalTrials.gov, number NCT02173002.

Role of the funding source

The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

Between Sept 9, 2014, and May 18, 2015, about 3000 outpatients with inflammatory bowel disease were asked to participate in this study, of whom 17% did not meet the inclusion criteria, 41% did not return the invitation letter, and 12% were not interested, providing reasons such as “too busy”, “participating in other studies”, “not now”, “too much confrontation with the disease”, and “impersonality of telemedicine” (figure 2). 909 eligible patients provided written informed consent and were randomly assigned, 465 to the telemedicine group and 444 to the standard care group. Neither protocol deviations nor adverse events related to use of the telemedicine intervention occurred. The baseline characteristics of the two study groups were similar and were representative of the general inflammatory bowel disease population in demographic characteristics and disease activity (table 1).²⁸ At the end of the 12 month study period, 438 (94%) patients in the telemedicine group continued to use the telemedicine system and 443 (99.8%) in the standard care group continued their routine follow-up visits in the same hospital

Figure 2. Trial profile.

(figure 2). At baseline, 382 (82%) patients in the telemedicine group and 369 (83%) in the standard care group completed the paper questionnaires about perceived quality of care, medication adherence, quality of life, self-efficacy, disease-related and medication-related knowledge, and smoking behaviour. At 12 months, these questionnaires were completed by 340 (73%) patients in the telemedicine group and 331 (75%) patients in the standard care group. All randomised patients were included in the analyses (intention-to-treat population). One patient in the telemedicine group died because of mucinous colorectal cancer, which was deemed to be unrelated to the study intervention.

At 12 months, the mean number of outpatient visits to the gastroenterologist was significantly lower in the telemedicine group than in the standard care group (1.26 [SD

Table 1. Baseline characteristics

	MyIBDcoach (n=465)	Standard care (n=444)
Centre, N		
Maastricht University Medical Centre	133	131
Leiden University Medical Centre	144	152
Zuyderland Medical Centre Sittard	117	102
St. Antonius Hospital Nieuwegein	71	59
Gender, N (%)		
Male	194 (41.7)	180 (40.5)
Female	271 (58.3)	264 (59.5)
Age at diagnosis, mean (SD)	30.7 (13.5)	30.4 (13.6)
Age at inclusion, mean (SD)	44.0 (14.1)	44.1 (14.2)
Disease duration (years), mean (SD)	12.8 (10.4)	13.1 (10.8)
Phenotype, N (%)		
Crohn's disease	282 (60.6)	262 (59.0)
Ileal	87/282 (30.9)	68/262 (26.0)
Colonic	67/282 (23.8)	63/262 (24.0)
Ileocolonic	128/282 (45.4)	131/262 (50.0)
Upper gastrointestinal modifier	34/282 (12.1)	26/262 (9.9)
Nonpenetrating, nonstricturing, B1	169/282 (59.9)	152/262 (58.0)
Stricturing, B2	76/282 (27.0)	70/262 (26.7)
Penetrating, B3	37/282 (13.1)	40/262 (15.3)
Perianal disease modifier	67/282 (23.8)	62/262 (23.7)
Ulcerative colitis	183 (39.4)	182 (41.0)
Proctitis, E1	26/183 (14.2)	27/182 (14.8)
Left sided, E2	81/183 (44.3)	70/182 (38.5)
Pancolitis, E3	76/183 (41.5)	85/182 (46.7)
Treatment (N), (%)		
No medication/mesalazine	173/465 (37.2)	147/444 (33.1)
Immunosuppressives	122/465 (26.2)	131/444 (29.5)
Biologics	170/465 (36.6)	166/444 (37.4)
Baseline disease activity, N (%)		
Remission	394/465 (84.7)	380/444 (85.6)
Active disease	71/465 (15.3)	64/444 (14.4)
Smokers, N (%)		
Non-smoker	157/379 (41.4)	159/367 (43.3)
Active smoker	65/379 (17.2)	50/367 (13.6)
Ex-smoker	157/379 (41.4)	158/367 (43.1)
Education, N (%)		
Academic	54/379 (14.2)	49/367 (13.4)
Higher vocational education	103/379 (27.2)	98/367 (26.7)
Intermediate vocational education	160/379 (42.2)	157/367 (42.8)
Secondary education	56/379 (14.8)	55/367 (15.0)
Primary education	6/379 (1.6)	8/367 (2.1)

1.18] in the telemedicine group vs 1.98 [1.19] in the standard care group; estimated intervention effect -0.72 [95% CI -0.87 to -0.56]; $p < 0.0001$; table 2). Outpatient visits to the nurse, however, did not differ significantly between groups (table 2). The total number of outpatient visits (gastroenterologist or nurse) was significantly lower in the telemedicine group than in the standard care group (1.55 [1.50] in the telemedicine group vs 2.34 [1.64] in the standard care group; estimated intervention effect -0.79 [-0.98 to -0.59]; $p < 0.0001$). The mean number of telephone consultations with the gastroenterologist was also significantly lower in the telemedicine group than in the standard care group, but the mean number of telephone consultations with the nurse did not differ significantly (table 2). These results were largely consistent across patients with Crohn's disease and ulcerative colitis, those treated in academic and non-academic settings, men and women, all age categories, all medication categories, and all disease duration categories (supplementary table 1). However, for patients in academic settings, the mean number of outpatient visits to the nurse was lower in the telemedicine group than in the standard care group (supplementary table 1).

Table 2. The effects of myIBDcoach on healthcare utilisation compared to standard care.

	MyIBDcoach n=465	Standard care n=444			
	Mean (SD)	Mean (SD)	Estimated intervention effect ^a	95% CI	P-value
Outpatient visits					
Gastroenterologist	1.26 (1.18)	1.98 (1.19)	-0.72	-0.87, -0.56	<0.001
Nurse	0.29 (0.68)	0.36 (0.84)	-0.07	-0.17, 0.03	0.173
Total	1.55 (1.50)	2.34 (1.64)	-0.79	-0.98, -0.59	<0.001
Phone consultations					
Gastroenterologist	0.58 (0.98)	0.84 (1.11)	-0.26	-0.40, -0.12	<0.001
Nurse	0.70 (1.59)	0.74 (1.90)	-0.08	-0.30, 0.13	0.448
Total	1.28 (2.06)	1.57 (2.44)	-0.34	-0.63, -0.06	0.018

^a Adjusted for centre, treatment, phenotype, age, gender, disease duration, disease activity at baseline, smoking, and educational level. Bootstrap CIs were similar to those presented here. The estimated intervention effect, 95% CI and p-value were obtained after multiple imputation.

Patients in the telemedicine and standard care groups reported similar and high scores for quality of care at 12 months (8.16 [SD 1.37] vs 8.27 [1.28], respectively; estimated intervention effect 0.10 [95% CI -0.13 to 0.32]; $p = 0.411$; table 3). Results were similar in patients with Crohn's disease and ulcerative colitis, those treated in academic and non-academic settings, men and women, and in all age and disease duration categories. Patients in the telemedicine group using biological therapies reported lower scores for quality of care than did patients in the standard care group ($p = 0.037$; supplementary table 2).

Over the 12 month follow-up period, the mean numbers of flares, courses of corticosteroid treatment, emergency visits, and inflammatory bowel disease-related surgeries did not differ significantly between the two groups (table 4). The mean number of hospital admissions was significantly lower in the telemedicine group than in the standard care group (16 unique patients admitted to hospital in the telemedicine group vs 29 in the standard care group; estimated intervention effect -0.05 [95% CI -0.10 to 0.00]; $p=0.046$). Reasons for admission to hospital included exacerbation of disease (six patients in the telemedicine group vs eight in the standard care group), surgery (eight vs ten), complications of the disease (ie, intestinal obstruction, active perianal disease, or ostomy dysfunction; six vs 14), medication side-effects (one vs six), and abdominal pain without evidence for active disease (none vs five). Analyses per subtype showed no significant differences between groups in numbers of flares, courses of corticosteroid treatment, emergency visits, and inflammatory bowel disease-related surgeries (supplementary

Table 3. The effects of myIBDcoach on patient-reported outcomes compared to standard care.

	MyIBDcoach		Standard care		Estimated intervention effect ^a	95% CI	P-value
	n	Mean score (SD)	n	Mean score (SD)			
Quality of care							
Baseline	382	8.25 (1.24)	369	8.26 (1.05)	0.10	-0.13, 0.32	0.411
12 months	340	8.16 (1.37)	331	8.27 (1.28)			
Medication adherence							
Baseline	382	6.52 (1.76)	369	6.67 (1.70)	0.46	0.22, 0.70	<0.001
12 months	340	7.01 (1.40)	331	6.77 (1.61)			
Quality of life							
Baseline	382	53.34 (10.29)	369	53.42 (9.95)	1.22	-0.04, 2.49	0.057
12 months	340	54.44 (9.05)	331	53.71 (9.87)			
Self-efficacy							
Baseline	382	224.16 (64.04)	369	222.14 (36.88)	2.45	-6.05, 10.94	0.572
12 months	340	223.35 (32.11)	331	220.28 (35.08)			
Knowledge on inflammatory bowel disease							
Baseline	383	7.66 (1.30)	369	7.57 (1.36)	0.20	-0.19, 0.41	0.074
12 months	340	8.17 (1.16)	331	7.84 (1.47)			
Knowledge on medication							
Baseline	383	7.34 (1.51)	369	7.29 (1.44)	0.14	-0.09, 0.37	0.235
12 months	340	7.75 (1.58)	331	7.58 (1.51)			

Quality of care was assessed by a VAS-scale, medication adherence by the MMAS-8²⁵, quality of life by the SIBDQ²⁶, and self-efficacy by the IBD-SES²⁷. ^aAdjusted for centre, treatment, phenotype, age, gender, disease duration, disease activity at baseline, smoking, educational level, and baseline patient-reported values. Bootstrap CIs were similar to those presented here. The estimated intervention effect, 95% CI and p-value were obtained from linear mixed models based on the likelihood approach for missing outcome data.

table 3). However, patients in the telemedicine group with Crohn's disease (estimated intervention effect -0.09 [95% CI -0.17 to -0.02]; $p=0.012$), or using biological therapies (-0.12 [-0.22 to -0.02]; $p=0.025$), or with a disease duration of more than 10 years (-0.08 [-0.17 to 0.00]; $p=0.045$) were less often admitted to the hospital than their respective controls. Adherence to medication at the end of the trial was significantly higher in the telemedicine group than in the standard care group (table 3). Both groups reported normal values for quality of life and high scores for self-efficacy and disease-related and medication-related knowledge, with no significant differences between groups (table 3). Smoking behaviour at the end of the study period did not differ between groups (odds ratio 0.81 [95% CI 0.33 – 1.96]; $p=0.633$, supplementary table 4).

Table 4. The effects of myIBDcoach on disease outcomes compared to standard care.

	MyIBDcoach n=465	Standard care n=444			
	Mean, SD	Mean, SD	Estimated intervention effect ^a	95% CI	P-value
Flares	0.19, 0.42	0.19, 0.44	-0.01	-0.06, 0.05	0.819
Corticosteroid courses	0.10, 0.33	0.12, 0.37	-0.02	-0.07, 0.02	0.322
Hospital admissions	0.05, 0.28	0.10, 0.43	-0.05	-0.10, 0.00	0.046
Emergency visits	0.07, 0.35	0.10, 0.54	-0.03	-0.09, 0.03	0.366
Inflammatory bowel disease- related surgeries	0.03, 0.16	0.03, 0.16	0.00	-0.02, 0.02	0.786

Adjusted for center, treatment, phenotype, age, gender, disease duration, disease activity at baseline, smoking, and educational level. Bootstrap CIs were similar to those presented here. The estimated intervention effect, 95% CI and p-value obtained after multiple imputation.

DISCUSSION

This pragmatic, randomised controlled trial compared a telemedicine system versus standard outpatient care for patients with inflammatory bowel disease, irrespective of disease course or treatment. Our findings showed that use of the telemedicine system resulted in a reduction in outpatient visits, telephone consultations, and admissions to hospital, and increased adherence to medication. Additionally, the telemedicine system was safe and patient-reported quality of healthcare remained high.

Ameliorating quality of care for chronic diseases has been defined as improving long-term disease outcomes, creating a healthier population, and reducing healthcare costs.^{12,29} Our results showed that the use of a telemedicine system reduced the number of outpatient visits, while enabling tight follow-up of disease activity. Disease monitoring with the telemedicine system was safe, because there were no significant differences between groups in numbers of flares, corticosteroid courses, emergency visits, and surgeries. Moreover, use of the telemedicine system resulted in fewer hospital admissions.

These results are in line with the improved care and monitoring with telemedicine in other (relapsing-remitting) chronic diseases, such as chronic obstructive pulmonary disease and heart failure.^{14,15} However, those studies were done in fairly small and specific patient subgroups, with differences in follow-up times and outcome measures, resulting in inconsistent results. This inconsistency complicates the ability to draw firm conclusions on the effectiveness of telemedicine in larger real-world populations.

To our knowledge, myIBDcoach is the first telemedicine tool for all subtypes of inflammatory bowel disease, irrespective of phenotype, setting, medical treatment, or disease severity. Two previous randomised controlled trials assessed the effect of telemedicine on the management of subtypes of inflammatory bowel disease with mild disease.^{19,20} One trial, in 47 patients with ulcerative colitis, compared self-testing of disease activity by questionnaires and weight measurements with standard care, but found no differences between groups in disease outcomes.²⁰ The other trial, in 333 patients with mild-to-moderate ulcerative colitis who were being treated with mesalazine, showed that tight monitoring of disease activity and personalised treatment strategies reduced outpatient visits compared with usual care.¹⁹ By contrast with our findings, disease activity, relapse frequency, and rates of hospital admission and surgery did not differ in the two groups. However, active self-management shortened relapse duration. As in our study, telemedicine improved adherence to treatment, but we did not find differences in quality of life, self-efficacy, and disease-related and medication-related knowledge, which might have been caused by the high baseline scores on these questionnaires in both the telemedicine and standard care groups.^{26,27} Our study was done in four centres with well organised and accessible outpatient clinics with dedicated nurses and an e-mail and telephone consultation structure. As a consequence, rates of outpatient visits were relatively low compared with other European clinics,³⁰ suggesting that the effect of the telemedicine system on the reduction of outpatient visits might be larger in other clinics.

In addition to disease activity, myIBDcoach also monitors factors that affect disease outcomes, including adherence to treatment, psychosocial factors, smoking, and nutrition. Awareness of these factors and development of standard intervention procedures and educational programmes can further improve the long-term outcome of patients with inflammatory bowel disease. For example, improved medication adherence has been found to improve long-term disease outcomes.^{7,8} The telemedicine system offers interactive e-learning modules on various subjects, allowing patients to review modules when they or their healthcare providers consider it desirable. The system also registers patient-reported outcome measures on quality of life and work productivity, and quality metrics for value-based healthcare following the International Consortium for Health Outcomes Measurement recommendations. These findings can immediately be visualised and reported to both individual users and their healthcare providers in a personal

care plan. Hospitals with value-based healthcare programmes could use telemedicine systems to measure patient-reported outcome measures and patient-reported experience measures.¹⁰ Furthermore, systematic registration of quality metrics and aggregation of these metrics from different practices might improve quality of care and reduce practice variability.^{11,31}

The main strength of our study was its randomised and pragmatic design. An unselected heterogeneous group of patients, clinicians, and clinical practices were included to maximise the applicability of these results to everyday practice. A potential weakness of the study design was that neither patients nor clinicians were masked to group assignments. We discussed giving all patients the telemedicine system while only monitoring patients in the intervention group. However, we felt that it was not ethical to ask the control group to use the telemedicine system without monitoring possibly relevant information resulting from red flags, nor to instruct those patients to plan follow-up visits only when necessary rather than traditionally booked appointments. The fairly short follow-up period can also be considered a limitation of the study. Intervention trials with 12 month follow-up are, however, regarded sufficient for maintenance drug therapy for registration purposes. Nevertheless, clinicians and patients require time to adapt to an altered clinical workflow. Interventions based on aberrant patient-reported outcome measure values require new procedures and protocols. Trials with longer follow-up periods are required to determine whether the telemedicine system can control costs and improve long-term disease outcomes.

Although telemedicine shows many benefits in managing patients with chronic diseases, few “tele-systems” have been implemented in everyday care. Among the reasons are the absence of a framework for the development, evaluation, and implementation of eHealth interventions;¹⁸ a disconnect between users and developers of health IT systems;³² the development of telemedicine programmes aimed at specific subgroups of patients with regard to treatment regimen, disease severity, or healthcare setting;^{7,19–21} and financial hurdles such as reimbursement of telemedicine consultations by insurance companies. To overcome these barriers, myIBDcoach was developed and pilot-tested with a structured iterative process and through close collaboration between the developer, delegates from the Dutch inflammatory bowel disease patient organisation (CCUVN), nurses, and gastroenterologists working in secondary and tertiary referral centres.²² Additionally, we deliberately assessed the effects of telemedicine on quality of care in a large unselected population of patients with all subtypes of inflammatory bowel disease, representative of a general inflammatory bowel disease population in a specialised care setting,²⁸ thereby providing external validity of the results for entire populations of patients with inflammatory bowel disease. Although this study was done in patients with inflammatory bowel disease, the results suggest that telemedicine can

measure and improve the quality and value of healthcare in patients with other chronic relapsing-remitting diseases.

Our results show that telemedicine with myIBDcoach was safe, reduced outpatient visits and hospital admissions, and improved adherence to medication with similar patient-reported quality of care compared with standard care. These results were consistent across different subtypes of inflammatory bowel disease. This telemedicine tool systematically monitors and registers disease activity and factors affecting disease, patient-reported outcome measures, drug side-effects, and quality metrics. In an era of healthcare cost reduction and a rising incidence of inflammatory bowel disease, telemedicine systems could be a valuable tool for reorganising inflammatory bowel disease care towards more personalised and value-based healthcare.

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Supplementary table 1. The effects of myIBDcoach on healthcare utilisation compared to standard care per subgroup.

	MyIBDcoach			Controls			Estimated intervention effect ^a	95% CI	P-value
	n	Mean (SD)	n	Mean (SD)					
Outpatient visits									
Gastroenterologist									
Crohn's disease	282	1.37 (1.24)	262	2.05 (1.23)		-0.66	-0.86, -0.46	<0.001	
Ulcerative colitis	183	1.09 (1.04)	182	1.88 (1.14)		-0.80	-1.04, -0.56	<0.001	
Academic	277	1.33 (1.20)	283	1.98 (1.16)		-0.67	-0.87, -0.47	<0.001	
Non-academic	188	1.16 (0.14)	161	1.98 (2.26)		-0.81	-1.06, -0.56	<0.001	
Female	271	1.32 (1.15)	264	2.02 (1.26)		-0.68	-0.88, -0.48	<0.001	
Male	194	1.11 (1.18)	180	1.93 (1.09)		-0.78	-1.02, -0.54	<0.001	
Age 18-30 years	104	1.36 (1.17)	99	1.93 (1.24)		-0.54	-0.87, -0.22	0.002	
Age 31-50 years	204	1.19 (1.07)	188	1.98 (1.51)		-0.80	-1.03, -0.56	<0.001	
Age >50 years	157	1.21 (1.29)	157	2.01 (1.22)		-0.73	-0.99, -0.47	<0.001	
No medication/mesalazine	173	1.25 (1.20)	147	1.93 (1.11)		-0.73	-0.99, -0.47	<0.001	
Immunosuppressives	122	1.12 (1.11)	131	2.02 (1.32)		-0.81	-1.10, -0.52	<0.001	
Biological therapy	170	1.30 (1.18)	166	2.00 (1.17)		-0.62	-0.87, -0.37	<0.001	
Disease duration 0-5 years	152	1.21 (1.16)	139	2.98 (1.22)		-0.77	-1.04, -0.50	<0.001	
Disease duration 6-10 years	90	1.31 (1.33)	80	1.93 (1.12)		-0.63	-0.99, -0.27	<0.001	
Disease duration >10 years	223	1.22 (1.11)	225	2.00 (1.21)		-0.72	-0.94, -0.50	<0.001	
Nurse									
Crohn's disease	282	0.35 (0.73)	262	0.37 (0.82)		-0.02	-0.15, 0.11	0.769	
Ulcerative colitis	183	0.21 (1.57)	182	0.35 (0.86)		-0.14	-0.29, 0.01	0.072	
Academic	277	0.24 (0.59)	283	0.39 (0.81)		-0.16	-0.28, -0.03	0.014	
Non-academic	188	0.37 (0.78)	161	0.30 (0.89)		-0.07	-0.09, 0.23	0.388	
Female	271	0.34 (0.75)	264	0.39 (0.88)		-0.06	-0.19, 0.69	0.368	
Male	194	0.22 (0.52)	180	0.32 (0.78)		-0.08	-0.24, 0.07	0.298	
Age 18-30 years	104	0.45 (0.93)	99	0.37 (0.95)		0.04	-0.17, 0.25	0.706	
Age 31-50 years	204	0.25 (0.55)	188	0.38 (0.82)		-0.12	-0.27, 0.03	0.106	
Age >50 years	157	0.23 (0.60)	157	0.33 (0.79)		-0.07	-0.24, 1.00	0.403	
No medication/mesalazine	173	0.38 (0.81)	147	0.29 (0.88)		0.00	-0.16, 0.17	0.986	

Supplementary table 1. The effects of myIBDcoach on healthcare utilisation compared to standard care per subgroup. (*continued*)

	MyIBDcoach			Controls			Estimated intervention effect ^a	95% CI	P-value
	n	Mean (SD)	n	Mean (SD)	Mean (SD)	Mean (SD)			
Immunosuppressives	122	0.23 (0.51)	131	0.36 (0.81)			-0.05	-0.23, 0.14	0.619
Biological therapy	170	0.24 (0.60)	166	0.43 (0.82)			-0.16	-0.32, -0.00	0.054
Disease duration 0-5 years	152	0.35 (0.78)	139	0.41 (0.86)			-0.09	-0.26, 0.09	0.333
Disease duration 6-10 years	90	0.26 (0.65)	80	0.41 (0.96)			-0.15	-0.38, 0.08	0.207
Disease duration >10 years	223	0.25 (0.59)	225	0.31 (0.78)			-0.03	-0.17, 0.11	0.689
Total									
Crohn's disease	282	1.72 (1.58)	262	2.42 (1.68)			-0.68	-0.94, -0.43	<0.001
Ulcerative colitis	183	1.29 (1.34)	182	2.22 (1.57)			-0.94	-1.25, -0.63	<0.001
Academic	277	1.57 (1.45)	283	2.37 (1.61)			-0.83	-1.08, -0.57	<0.001
Non-academic	188	1.52 (1.57)	161	2.28 (1.69)			-0.74	-1.06, -0.41	<0.001
Female	271	1.66 (1.53)	264	2.41 (1.74)			-0.74	-1.00, -0.48	<0.001
Male	194	1.32 (1.38)	180	2.25 (1.48)			-0.85	-1.16, -0.55	<0.001
Age 18-30 years	104	1.81 (1.64)	99	2.30 (1.71)			-0.50	-0.92, -0.09	0.019
Age 31-50 years	204	1.44 (1.29)	188	2.36 (1.66)			-0.91	-1.22, -0.61	<0.001
Age >50 years	157	1.43 (1.59)	157	2.34 (1.58)			-0.80	-1.14, -0.47	<0.001
No medication/mesalazine	173	1.64 (1.53)	147	2.21 (1.54)			-0.73	-1.07, -0.40	<0.001
Immunosuppressives	122	1.35 (1.39)	131	2.37 (1.79)			-0.85	-1.22, -0.48	<0.001
Biological therapy	170	1.53 (1.48)	166	2.43 (1.60)			-0.79	-1.11, -0.46	<0.001
Disease duration 0-5 years	152	1.56 (1.62)	139	2.39 (1.67)			-0.85	-1.20, -0.50	<0.001
Disease duration 6-10 years	90	4.58 (1.60)	80	2.34 (1.62)			-0.78	-1.24, 0.31	0.001
Disease duration >10 years	223	1.47 (1.33)	225	2.31 (1.63)			-0.75	-1.03, -0.47	<0.001
Phone consultations									
Gastroenterologist									
Crohn's disease	282	0.65 (1.06)	262	0.87 (1.10)			-0.21	-0.39, -0.02	0.027
Ulcerative colitis	183	0.48 (0.83)	182	0.80 (1.13)			-0.34	-0.55, -0.12	0.002
Academic	277	0.61 (1.01)	283	0.80 (1.08)			-0.19	-0.37, -0.01	0.036
Non-academic	188	0.55 (0.94)	161	0.91 (1.17)			-0.36	-0.58, -0.13	0.002
Female	271	0.58 (0.97)	264	0.91 (1.18)			-0.31	-0.49, -0.13	0.001

Supplementary table 1. The effects of myIBDcoach on healthcare utilisation compared to standard care per subgroup. (continued)

	MyIBDcoach		Controls		Estimated intervention effect ^a	95% CI	P-value
	n	Mean (SD)	n	Mean (SD)			
Male	194	0.53 (0.97)	180	0.74 (1.00)	-0.20	-0.41, -0.02	0.081
Age 18-30 years	104	0.57 (0.98)	99	0.74 (1.08)	-0.13	-0.43, 0.17	0.382
Age 31-50 years	204	0.47 (0.77)	188	0.85 (1.08)	-0.35	-0.56, -0.14	0.001
Age >50 years	157	0.66 (1.17)	157	0.88 (1.17)	-0.13	-0.47, 0.01	0.059
No medication/mesalazine	173	0.49 (0.87)	147	0.88 (1.18)	-0.37	-0.61, -0.14	0.002
Immunosuppressives	122	0.59 (0.90)	131	0.75 (0.99)	-0.17	-0.43, 0.10	0.209
Biological therapy	170	0.60 (1.10)	166	0.87 (1.14)	-0.22	-0.44, 0.01	0.058
Disease duration 0-5 years	152	0.63 (1.11)	139	0.70 (1.11)	-0.07	-0.32, 0.17	0.549
Disease duration 6-10 years	90	0.49 (0.76)	80	0.76 (1.06)	-0.23	-0.55, 0.10	0.169
Disease duration >10 years	223	0.53 (0.94)	225	0.95 (1.21)	-0.39	-0.59, -0.20	<0.001
Nurse							
Crohn's disease	282	0.76 (1.69)	262	0.71 (1.86)	0.02	-0.26, 0.30	0.913
Ulcerative colitis	183	0.60 (1.40)	182	0.77 (1.96)	-0.23	-0.57, 0.11	0.186
Academic	277	0.31 (0.80)	283	0.41 (0.87)	-0.11	-0.38, 0.17	0.436
Non-academic	188	1.27 (2.18)	161	1.31 (2.85)	-0.04	-0.34, 0.30	0.808
Female	271	0.86 (1.80)	264	0.86 (2.25)	-0.09	-0.37, 0.19	0.519
Male	194	0.49 (1.17)	180	0.55 (1.20)	-0.07	-0.41, 0.27	0.682
Age 18-30 years	104	1.17 (2.25)	99	0.71 (1.55)	0.34	-0.11, 0.80	0.141
Age 31-50 years	204	0.64 (1.40)	188	0.85 (2.13)	-0.26	-0.59, 0.07	0.118
Age >50 years	157	0.50 (1.19)	157	0.62 (1.80)	-0.15	-0.52, 0.22	0.428
No medication/mesalazine	173	0.88 (1.74)	147	0.84 (2.20)	-0.08	-0.44, 0.29	0.675
Immunosuppressives	122	0.78 (1.90)	131	0.90 (2.28)	-0.12	-0.52, 0.29	0.578
Biological therapy	170	0.48 (1.07)	166	0.51 (1.09)	-0.07	-0.42, 0.29	0.715
Disease duration 0-5 years	152	0.98 (2.06)	139	0.92 (2.36)	0.00	-0.38, 0.39	0.987
Disease duration 6-10 years	90	0.69 (1.53)	80	0.86 (1.83)	-0.19	-0.69, 0.31	0.452
Disease duration >10 years	223	0.53 (1.15)	225	0.58 (1.57)	-0.11	-0.41, 0.20	0.499
Total							
Crohn's disease	282	1.41 (2.21)	262	1.58 (2.48)	-0.19	-0.56, 0.17	0.307

Supplementary table 1. The effects of myIBDcoach on healthcare utilisation compared to standard care per subgroup. (*continued*)

	MyIBDcoach		Controls			Estimated intervention effect ^a	95% CI	P-value
	n	Mean (SD)	n	Mean (SD)				
Ulcerative colitis	183	1.08 (1.76)	182	1.57 (2.41)		-0.56	-1.00, 0.12	0.013
Academic	277	0.92 (1.40)	283	1.21 (1.46)		-0.30	-0.66, -0.06	0.103
Non-academic	188	1.82 (2.66)	161	2.22 (3.50)		-0.40	-0.85, 0.06	0.088
Female	271	1.44 (2.23)	264	1.77 (2.83)		-0.40	-0.77, -0.03	0.035
Male	194	1.02 (1.02)	180	1.28 (1.70)		-0.27	-0.71, 0.18	0.241
Age 18-30 years	104	1.74 (2.77)	99	1.44 (1.97)		0.21	-0.39, 0.81	0.492
Age 31-50 years	204	1.11 (1.73)	188	1.70 (2.73)		-0.61	-1.04, -0.18	0.006
Age >50 years	157	1.16 (1.82)	157	1.50 (2.36)		-0.38	-0.86, 0.11	0.126
No medication/mesalazine	173	1.36 (2.17)	147	1.72 (2.76)		-0.45	-0.93, 0.03	0.064
Immunosuppressives	122	1.37 (2.33)	131	1.65 (2.86)		-0.29	-0.82, 0.25	0.299
Biological therapy	170	1.09 (1.64)	166	1.38 (1.66)		-0.28	-0.75, 0.18	0.231
Disease duration 0-5 years	152	1.61 (2.59)	139	1.62 (1.62)		-0.07	-0.57, 0.43	0.780
Disease duration 6-10 years	90	1.18 (1.76)	80	1.63 (2.26)		-0.42	-1.08, 0.24	0.213
Disease duration >10 years	223	1.06 (1.65)	225	1.53 (2.09)		-0.50	-0.90, -0.09	0.016

^a Adjusted for centre, phenotype, treatment, age, gender, disease duration, disease activity at baseline, smoking, and educational level. Bootstrap CIs were similar to those presented here. The estimated intervention effect, 95%CI and p-value were obtained after multiple imputation.

Supplementary table 2. The effects of myIBDcoach on patient-reported quality of care compared to standard care per subgroup.

	MyIBDcoach		Standard care		Estimated intervention effect ^a	95% CI	P-value
	n	Mean score (SD)	n	Mean score (SD)			
Crohn's disease							
Baseline	207	8.14 (1.32)	206	8.31 (1.00)	0.04	-0.26, 0.34	0.796
12 months	172	8.27 (1.34)	167	8.22 (1.43)			
Ulcerative colitis							
Baseline	143	8.51 (0.95)	138	8.15 (1.12)	0.16	-0.40, 0.18	0.368
12 months	131	8.23 (1.37)	117	8.34 (1.04)			
Academic							
Baseline	198	8.15 (1.35)	215	8.19 (1.09)	0.19	-0.11, 0.49	0.211
12 months	176	8.22 (1.38)	185	8.27 (1.30)			
Non-academic							
Baseline	152	8.47 (0.93)	129	8.33 (1.00)	-0.05	-0.41, 0.31	0.783
12 months	127	8.30 (1.33)	99	8.28 (1.25)			
Female							
Baseline	207	8.25 (1.12)	207	8.26 (1.05)	0.08	-0.21, -0.38	0.581
12 months	183	8.27 (1.40)	168	8.22 (1.31)			
Male							
Baseline	143	8.20 (1.30)	137	8.22 (1.07)	0.12	-0.24, 0.47	0.529
12 months	120	8.23 (1.27)	116	8.35 (1.24)			
Age 18-30 years							
Baseline	79	8.08 (1.88)	71	8.14 (0.95)	-0.18	-0.68, 0.31	0.467
12 months	65	8.28 (1.17)	59	8.02 (1.34)			
Age 31-50 years							
Baseline	145	8.29 (1.30)	140	8.22 (1.09)	-0.00	-0.35, 0.36	0.983
12 months	126	8.32 (1.19)	122	8.24 (1.40)			
Age > 50 years							
Baseline	126	8.42 (1.06)	133	8.33 (1.07)	0.35	-0.02, 0.72	0.067
12 months	112	8.16 (1.61)	103	8.45 (1.07)			
No medication/ mesalamines							
Baseline	135	8.27 (1.31)	119	8.17 (1.08)	0.05	-0.34, 0.44	0.804
12 months	109	8.15 (1.62)	95	8.29 (1.14)			
Immunosuppressives							
Baseline	92	8.48 (1.01)	101	8.19 (0.93)	-0.26	-0.69, 0.16	0.221
12 months	85	8.49 (1.02)	83	8.06 (1.56)			
Biological therapy							
Baseline	123	8.17 (1.19)	124	8.35 (1.12)	0.40	0.02, 0.77	0.037
12 months	109	8.17 (1.28)	106	8.43 (1.14)			

Supplementary table 2. The effects of myIBDcoach on patient-reported quality of care compared to standard care per subgroup. (*continued*)

	MyIBDcoach		Standard care		Estimated intervention effect ^a	95% CI	P-value
	n	Mean score (SD)	n	Mean score (SD)			
Disease duration 0-5 years							
Baseline	121	8.12 (1.37)	104	8.32 (0.92)	0.20	-0.21, 0.61	0.334
12 months	96	8.30 (1.03)	86	8.36 (1.28)			
Disease duration 6-10 years							
Baseline	66	8.32 (1.09)	56	8.25 (1.04)	-0.41	-0.97, 0.16	0.157
12 months	56	8.20 (1.09)	44	7.92 (1.59)			
Disease duration >10 years							
Baseline	163	8.40 (1.09)	184	8.20 (1.13)	0.18	-0.14, 0.50	0.261
12 months	151	8.24 (1.61)	154	8.32 (1.17)			

Patient-reported quality of care was assessed by a VAS-scale. ^aAdjusted for centre, treatment, phenotype, age, gender, disease duration, disease activity at baseline, smoking, educational level, and baseline patient-reported quality of care. Bootstrap CIs were similar to those presented here. The estimated intervention effect, 95%CI and p-value were obtained from linear mixed models based on the likelihood approach for missing outcome data.

Supplementary table 3. The effects of myIBDcoach on disease outcomes compared to standard care per subgroup.

	MyIBDcoach			Controls			Estimated intervention effect ^a	95% CI	P-value
	n	Mean (SD)	n	Mean (SD)					
Flares									
Crohn's disease	282	1.37 (1.24)	262	2.05 (1.23)	-0.66	-0.86, -0.46	<0.001		
Ulcerative colitis	183	1.09 (1.04)	182	1.88 (1.14)	-0.80	-1.04, -0.56	<0.001		
Academic	277	1.33 (1.20)	283	1.98 (1.16)	-0.67	-0.87, -0.47	<0.001		
Non-academic	188	1.16 (0.14)	161	1.98 (2.26)	-0.81	-1.06, -0.56	<0.001		
Female	271	1.32 (1.15)	264	2.02 (1.26)	-0.68	-0.88, -0.48	<0.001		
Male	194	1.11 (1.18)	180	1.93 (1.09)	-0.78	-1.02, -0.54	<0.001		
Age 18-30 years	104	1.36 (1.17)	99	1.93 (1.24)	-0.54	-0.87, -0.22	0.002		
Age 31-50 years	204	1.19 (1.07)	188	1.98 (1.51)	-0.80	-1.03, -0.56	<0.001		
Age >50 years	157	1.21 (1.29)	157	2.01 (1.22)	-0.73	-0.99, -0.47	<0.001		
No medication/mesalazine	173	1.25 (1.20)	147	1.93 (1.11)	-0.73	-0.99, -0.47	<0.001		
Immunosuppressives	122	1.12 (1.11)	131	2.02 (1.32)	-0.81	-1.10, -0.52	<0.001		
Biological therapy	170	1.30 (1.18)	166	2.00 (1.17)	-0.62	-0.87, -0.37	<0.001		
Disease duration 0-5 years	152	1.21 (1.16)	139	2.98 (1.22)	-0.77	-1.04, -0.50	<0.001		
Disease duration 6-10 years	90	1.31 (1.33)	80	1.93 (1.12)	-0.63	-0.99, -0.27	<0.001		
Disease duration >10 years	223	1.22 (1.11)	225	2.00 (1.21)	-0.72	-0.94, -0.50	<0.001		
Corticosteroid courses									
Crohn's disease	282	0.35 (0.73)	262	0.37 (0.82)	-0.02	-0.15, 0.11	0.769		
Ulcerative colitis	183	0.21 (1.57)	182	0.35 (0.86)	-0.14	-0.29, 0.01	0.072		
Academic	277	0.24 (0.59)	283	0.39 (0.81)	-0.16	-0.28, -0.03	0.014		
Non-academic	188	0.37 (0.78)	161	0.30 (0.89)	-0.07	-0.09, 0.23	0.388		
Female	271	0.34 (0.75)	264	0.39 (0.88)	-0.06	-0.19, 0.69	0.368		
Male	194	0.22 (0.52)	180	0.32 (0.78)	-0.08	-0.24, 0.07	0.298		
Age 18-30 years	104	0.45 (0.93)	99	0.37 (0.95)	0.04	-0.17, 0.25	0.706		

Supplementary table 3. The effects of myIBDcoach on disease outcomes compared to standard care per subgroup. (continued)

	MyIBDcoach		Controls		Estimated intervention effect ^a	95% CI	P-value
	n	Mean (SD)	n	Mean (SD)			
Age 31-50 years	204	0.25 (0.55)	188	0.38 (0.82)	-0.12	-0.27, 0.03	0.106
Age >50 years	157	0.23 (0.60)	157	0.33 (0.79)	-0.07	-0.24, 1.00	0.403
No medication/mesalazine	173	0.38 (0.81)	147	0.29 (0.88)	0.00	-0.16, 0.17	0.986
Immunosuppressives	122	0.23 (0.51)	131	0.36 (0.81)	-0.05	-0.23, 0.14	0.619
Biological therapy	170	0.24 (0.60)	166	0.43 (0.82)	-0.16	-0.32, -0.00	0.054
Disease duration 0-5 years	152	0.35 (0.78)	139	0.41 (0.86)	-0.09	-0.26, 0.09	0.333
Disease duration 6-10 years	90	0.26 (0.65)	80	0.41 (0.96)	-0.15	-0.38, 0.08	0.207
Disease duration >10 years	223	0.25 (0.59)	225	0.31 (0.78)	-0.03	-0.17, 0.11	0.689
Hospital admissions							
Crohn's disease	282	1.72 (1.58)	262	2.42 (1.68)	-0.68	-0.94, -0.43	<0.001
Ulcerative colitis	183	1.29 (1.34)	182	2.22 (1.57)	-0.94	-1.25, -0.63	<0.001
Academic	277	1.57 (1.45)	283	2.37 (1.61)	-0.83	-1.08, -0.57	<0.001
Non-academic	188	1.52 (1.57)	161	2.28 (1.69)	-0.74	-1.06, -0.41	<0.001
Female	271	1.66 (1.53)	264	2.41 (1.74)	-0.74	-1.00, -0.48	<0.001
Male	194	1.32 (1.38)	180	2.25 (1.48)	-0.85	-1.16, -0.55	<0.001
Age 18-30 years	104	1.81 (1.64)	99	2.30 (1.71)	-0.50	-0.92, -0.09	0.019
Age 31-50 years	204	1.44 (1.29)	188	2.36 (1.66)	-0.91	-1.22, -0.61	<0.001
Age >50 years	157	1.43 (1.59)	157	2.34 (1.58)	-0.80	-1.14, -0.47	<0.001
No medication/mesalazine	173	1.64 (1.53)	147	2.21 (1.54)	-0.73	-1.07, -0.40	<0.001
Immunosuppressives	122	1.35 (1.39)	131	2.37 (1.79)	-0.85	-1.22, -0.48	<0.001
Biological therapy	170	1.53 (1.48)	166	2.43 (1.60)	-0.79	-1.11, -0.46	<0.001
Disease duration 0-5 years	152	1.56 (1.62)	139	2.39 (1.67)	-0.85	-1.20, -0.50	<0.001
Disease duration 6-10 years	90	4.58 (1.60)	80	2.34 (1.62)	-0.78	-1.24, 0.31	0.001
Disease duration >10 years	223	1.47 (1.33)	225	2.31 (1.63)	-0.75	-1.03, -0.47	<0.001

Supplementary table 3. The effects of myIBDcoach on disease outcomes compared to standard care per subgroup. (*continued*)

	MyIBDcoach			Controls			Estimated intervention effect ^a	95% CI	P-value
	n	Mean (SD)	n	Mean (SD)					
Emergency visits									
Gastroenterologist									
Crohn's disease	282	0.65 (1.06)	262	0.87 (1.10)		-0.21	-0.39, -0.02	0.027	
Ulcerative colitis	183	0.48 (0.83)	182	0.80 (1.13)		-0.34	-0.55, -0.12	0.002	
Academic	277	0.61 (1.01)	283	0.80 (1.08)		-0.19	-0.37, -0.01	0.036	
Non-academic	188	0.55 (0.94)	161	0.91 (1.17)		-0.36	-0.58, -0.13	0.002	
Female	271	0.58 (0.97)	264	0.91 (1.18)		-0.31	-0.49, -0.13	0.001	
Male	194	0.53 (0.97)	180	0.74 (1.00)		-0.20	-0.41, -0.02	0.081	
Age 18-30 years	104	0.57 (0.98)	99	0.74 (1.08)		-0.13	-0.43, 0.17	0.382	
Age 31-50 years	204	0.47 (0.77)	188	0.85 (1.08)		-0.35	-0.56, -0.14	0.001	
Age >50 years	157	0.66 (1.17)	157	0.88 (1.17)		-0.13	-0.47, 0.01	0.059	
No medication/mesalazine	173	0.49 (0.87)	147	0.88 (1.18)		-0.37	-0.61, -0.14	0.002	
Immunosuppressives	122	0.59 (0.90)	131	0.75 (0.99)		-0.17	-0.43, 0.10	0.209	
Biological therapy	170	0.60 (1.10)	166	0.87 (1.14)		-0.22	-0.44, 0.01	0.058	
Disease duration 0-5 years	152	0.63 (1.11)	139	0.70 (1.11)		-0.07	-0.32, 0.17	0.549	
Disease duration 6-10 years	90	0.49 (0.76)	80	0.76 (1.06)		-0.23	-0.55, 0.10	0.169	
Disease duration >10 years	223	0.53 (0.94)	225	0.95 (1.21)		-0.39	-0.59, -0.20	<0.001	

Supplementary table 3. The effects of myIBDcoach on disease outcomes compared to standard care per subgroup. (continued)

	MyIBDcoach		Controls				
	n	Mean (SD)	n	Mean (SD)	Estimated intervention effect ^a	95% CI	P-value
Inflammatory bowel disease related surgeries							
Crohn's disease	282	0.03 (0.16)	262	0.04 (0.20)	-0.01	-0.04, 0.02	0.449
Ulcerative colitis	183	0.02 (0.15)	182	0.01 (0.07)	0.02	-0.01, 0.04	0.198
Academic	277	0.03 (0.16)	283	0.02 (0.16)	0.00	-0.03, 0.03	0.962
Non-academic	188	0.02 (0.15)	161	0.03 (0.17)	-0.01	-0.01, 0.03	0.766
Female	271	0.03 (0.16)	264	0.03 (0.17)	0.00	-0.03, 0.03	0.858
Male	194	0.02 (0.15)	180	0.02 (0.15)	0.00	-0.03, 0.03	0.884
Age 18-30 years	104	0.03 (0.16)	99	0.02 (0.14)	0.00	-0.04, 0.05	0.859
Age 31-50 years	204	0.06 (0.24)	188	0.03 (0.16)	0.00	-0.03, 0.03	0.851
Age >50 years	157	0.01 (0.10)	157	0.03 (0.18)	-0.01	-0.05, 0.03	0.789
No medication/mesalazine	173	0.02 (0.16)	147	0.01 (0.16)	-0.01	-0.04, 0.03	0.714
Immunosuppressives	122	0.02 (0.13)	131	0.03 (0.17)	-0.01	-0.05, 0.03	0.550
Biological therapy	170	0.03 (0.17)	166	0.02 (0.15)	0.01	-0.03, 0.03	0.579
Disease duration 0-5 years	152	0.03 (0.16)	139	0.03 (0.17)	0.00	-0.04, 0.04	0.936
Disease duration 6-10 years	90	0.06 (0.60)	80	0.00 (0.00)	0.04	-0.01, 0.10	0.132
Disease duration > 10 years	223	0.01 (0.10)	225	0.04 (0.19)	-0.03	-0.05, 0.00	0.085

^a Adjusted for centre, phenotype, treatment, age, gender, disease duration, disease activity at baseline, smoking, and educational level. Bootstrap CIs were similar to those presented here. The estimated intervention effect, 95%CI and p-value were obtained after multiple imputation.

Supplementary table 4. The effects of myIBDcoach on smoking behaviour compared to standard care.

	MyIBDcoach (n)	Standard care (n)	Odds ratio ^a	95% CI	p-value
Baseline ^b					
Active smoker	65	50			
Non-active smoker	314	317			
12 months ^c			0.81	0.33, 1.96	0.633
Active smoker	34	31			
Non-active smoker	304	298			

^aAdjusted for baseline smoking behaviour and educational level. ^b 86 and 77 values were missing at baseline in the myIBDcoach group and standard care group, respectively. ^c 127 and 115 values were missing at 12 months in the myIBDcoach group and standard care group, respectively.

Editorial commentary

Building evidence for care beyond
the medical centre

Thomas Ullman, Ashish Atreja

*Icahn School of Medicine at Mount Sinai, New York, NY 10029,
USA thomas.ullman@mssm.edu*

Digital health has been defined as the “convergence of the digital and genomic revolutions with health, healthcare, living, and society”.¹ The term is often used interchangeably with mHealth or mobile health because of the central role played by mobile devices. Remote patient monitoring and telemedicine constitute a subset of digital health technologies that enable monitoring of patients outside conventional clinical settings, such as in the comfort of their own homes. Evidence regarding the efficacy, effectiveness, economics, and clinical preferences of remote patient monitoring and telemedicine is growing in many chronic diseases, including heart failure, diabetes, chronic obstructive pulmonary disease, and stroke diagnosis, and in post-surgical care, rehabilitation, and behavioural medicine.^{2–5}

In *The Lancet*, Marin de Jong and colleagues⁶ report the results of a randomised trial among outpatients in two academic and two non-academic hospitals in the Netherlands showing substantial benefits of remote patient monitoring with patient use of a tablet or smartphone application called myIBDcoach compared with standard care in adults with inflammatory bowel disease. Designed to assist in lessening the burden of illness through regular monitoring away from the office, improve adherence to quality metrics, personalise care on the basis of patient-reported outcome measures, enhance remote communication with the care team, educate the patient through web-based learning tools, enable value-based healthcare, and even promote self-efficacy, the investigators achieved many of their stated aims. At 12 months, the use of the telemedicine system myIBDcoach resulted in significantly fewer outpatient visits to the gastroenterologist or nurse than standard care (1.55 [SD 1.50] vs 2.34 [1.64], respectively; difference -0.79 [95% CI -0.98 to -0.59]; $p < 0.0001$), fewer telephone consultations (1.28 [2.06] vs 1.57 [2.44]; $p = 0.018$), and improved medication adherence (mean score on the eight-item Morisky Medication Adherence Scale 7.01 [1.40] vs 6.77 [1.61]; $p = 0.0002$). The mean number of hospital admissions was also lower in patients using myIBDcoach than in those receiving standard care. No substantial differences between groups were noted in the mean number of corticosteroid courses, emergency visits, flares, or inflammatory bowel disease-related surgeries, or in quality-of-life scores. In view of the heterogeneity of these disorders and the complexity and variability of their treatments, these findings are a remarkable achievement.

Living with chronic illnesses such as Crohn’s disease and ulcerative colitis is no small challenge for affected patients. Pain, inconvenience, physical and emotional difficulties, and persistent reliance on family and friends for support constitute just a few of the regular hardships patients face—sometimes on a daily basis. Inadequately treated inflammatory bowel diseases can result in a substantially diminished quality of life, increased work disability (or absence from school), and an outsized financial burden, made up mostly of medication costs, hospital admissions, surgeries, and emergency care—some of the measures de Jong and colleagues captured with myIBDcoach. Usual

care for inflammatory bowel disease over the years has been limited to episodic office visits in which interim results and events are reviewed, and plans are made for adjusting care as needed on the basis of new information acquired at the visit—all in an effort to allow patients to pursue and live their lives outside of office and emergency visits, and with minimal impact on work or school. But why in 2017 should the primary site of care be the physician's office? If the goal is to unburden the patient, then most care in the modern, digital world should be provided at the convenience of the engaged patient. The hypothesis is that an increase in regular information sharing can lessen expensive care, achieve a personalised approach to treatment plans, optimise the use of expensive medications, accelerate the discontinuation of medicines that are no longer useful, and provide more freedom from burdensome office visits, emergency visits, and surgeries. de Jong and colleagues have achieved these outcomes with the use of myIBDcoach.

Without question, smartphone-based remote patient monitoring and telemedicine remain in their infancy. These technologies will proliferate and embed themselves in unpredictable and varying ways. de Jong and colleagues' demonstration of effectiveness closes some of the missing scientific evidence around these applications. We look forward to seeing new applications that will reduce symptoms, promote convenience, and keep patients well at home, work, or school.

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Chapter 6

Cost-effectiveness of telemedicine-directed specialised care versus standard care for inflammatory bowel disease: the myIBDcoach trial.

Marin de Jong, Annelies Boonen, Mariëlle Romberg-Camps,
Ad van Bodegraven, Nofel Mahmmod, Tineke Markus, Gerard Dijkstra,
Ad Masclee, Bjorn Winkens, Astrid van Tubergen, Daisy Jonkers,
Andrea van der Meulen-de Jong, Marieke Pierik

Submitted

ABSTRACT

Objective: Telemedicine is a powerful tool to monitor determinants and outcomes of health in chronic diseases and can contribute to quality and value of care. For inflammatory bowel diseases (IBD), telemedicine was found to reduce outpatient visits and hospital admissions. Since a full economic evaluation of telemedicine interventions in IBD is lacking, we evaluated the cost-utility of telemedicine versus standard care.

Design: A pragmatic multicentre randomised controlled trial was carried out in two academic and two non-academic hospitals in the Netherlands. In total, 909 IBD patients were randomised to telemedicine (n=465) or standard outpatient care (n=444) and followed for 12 months. Costs were measured from a societal perspective. Direct healthcare costs were based on actual resource utilisation. Indirect costs comprised self-reported hours sick leave from work, intervention costs (annual license fee of €40 per patient), and utility costs (assessed using EQ5D). Cost-utility and uncertainty were estimated using the non-parametric bootstrapping method.

Results: Telemedicine resulted in lower mean annual costs of €547/patient (95%CI, [€-1,029, €2,143]; mean costs of €9481 for standard care and €8924 for telemedicine) without changing quality adjusted life years (QALY). At the Dutch threshold of €80,000 per QALY, the intervention had a favorable incremental cost-effectiveness over standard care in 83% of replications and showed an incremental net monetary benefit of €707/patient (95%CI, [€-1,241, €2,544]).

Conclusion: Telemedicine with myIBDcoach was cost-effective in 83% of replications. This self-management tool enables continuous registration of quality indicators and (patient-reported) outcomes and is therefore promising to reorganise IBD care towards value-based healthcare.

INTRODUCTION

Improving quality of care is a continuous task for every healthcare professional and institution, and is especially challenging when increasing healthcare expenditures force professionals to constrain costs. Over the recent years, value-based healthcare has been considered a way forward to control costs while improving quality by emphasising the value for patients as the common goal of all stakeholders (patient, healthcare professional, insurance company, and society)¹. In this framework, regular measurement of clinical and patient-reported health outcomes is necessary. In a traditional healthcare organisation frequent monitoring of these outcomes is challenging due to time constraints and a further increase of the administrative burden. Telemedicine enables regular collection of health outcomes without disrupting the clinical workflow^{2,3}. However, no data are available regarding cost-effectiveness of telemedicine.

The inflammatory bowel disease (IBD), Crohn's disease (CD) and ulcerative colitis (UC), are debilitating, chronically relapsing, inflammatory disorders primarily affecting the gastrointestinal tract. As IBD is typically diagnosed in young people during the most productive years of their lives⁴ and requires life-long medical therapy and monitoring, the disease has a significant impact on patients' quality of life. It constitutes a high economic burden on society^{5,6}. Cost-of-illness studies report total annual healthcare costs in Western-European countries ranging from €6,338-€8,004 for CD and €3,600-€4,819 for UC patients^{6,7,8}. Today, the direct healthcare costs for IBD are mainly driven by medication costs, hospitalisations, and outpatient clinic visits, while diagnostic procedures and surgery account for a relatively small portion^{6,7,8}. In addition, productivity losses resulting from sick leave and work disability account for up to 50% of the total costs-of-illness in IBD⁷.

IBD care is traditionally organised by standard scheduled outpatient visits, with a frequency predominantly based on medical treatment, but independent of the occurrence of unpredictable flares^{9,10}. This might result in an inefficient and potentially costly way of medical resource use and patients' time. In addition, treatment strategies for IBD are shifting from mere management of symptoms towards tight and personalised control of intestinal inflammation and timely intervention if inflammation (re-)occurs in order to prevent structural bowel damage and eventually improve long-term disease outcome^{9,10,11}. This, together with the rising incidence of IBD, results in overburdened IBD clinics and escalating costs^{12,13}.

Implementation of telemedicine for IBD can improve efficiency of care, enable tight disease monitoring and registration of PROMs, and answers to patients' demands for more participation in disease management. A pragmatic randomised multicentre trial with the telemedicine tool myIBDcoach showed that personalised telemonitoring re-

duced the number of outpatient visits by 36% and the number of hospitalisations by 50%, while increasing adherence to medication when compared to standard care¹⁴.

Although this trial convincingly showed that the telemedicine tool reduced health-care utilisation, broad implementation is currently hindered by some barriers of which reimbursement is considered to be the key determinant³. Therefore, research focusing on economic evaluation of telemedicine interventions is warranted to aid decision makers in estimating the value of healthcare reorganisation towards reimbursement of telemedicine². The objective of this study was therefore to calculate, from a societal perspective, the cost-effectiveness of telemedicine with myIBDcoach compared to standard care for IBD patients.

METHODS

Study design and participants

The myIBDcoach study design and data collection are described previously¹⁴. In brief, this study was carried out in two academic and two non-academic hospitals in the Netherlands, each caring for 1,500–2,000 IBD patients, with one or two dedicated nurses or nurse specialists, as well as an e-mail and telephone consultation structure for patients to contact the IBD team. IBD patients, between 18 and 75 years of age, were eligible for inclusion when they had no history of an ileoanal pouch or ileorectal anastomosis. Illiterate patients, those unable to understand the informed consent form or those without internet access by computer, tablet or smartphone, were excluded. Patients were randomised in a 1:1 ratio to care via myIBDcoach (intervention group) or standard care (control group) and were followed for 12 months. The details of the telemedicine system myIBDcoach, which was designed in close collaboration with patients, have been described previously¹⁵. Besides telemonitoring of disease activity and disease-related aspects, such as nutrition, medication adherence, or smoking, myIBDcoach provides patient-tailored information, a personal care plan, and easy, accessible contact with the inflammatory bowel disease nurse. At baseline and after 12 months, all participants received a paper questionnaire regarding health-related quality of life, and work-productivity. Patients were involved in all stages of research and the development of myIBDcoach. At 12 months an additional questionnaire on healthcare utilisation (number of e-mail and phone consultations) was sent to the participants. The study has been approved by the Medical Ethics Committee of the Maastricht University Medical Centre+ and all subjects gave written informed consent prior to participation. This approval was applicable to all participating centres. This trial was registered at ClinicalTrials.gov (NCT02173002).

Clinical and demographic data

Demographic and clinical data, i.e. patient characteristics, disease phenotype, disease duration, baseline disease activity, were obtained from patients' electronic medical records.

Direct healthcare costs

Information on IBD-related healthcare utilisation over the 12-month study period, i.e. outpatient service, inpatient service, medication use, diagnostic procedures, and surgery, was collected from patients' electronic medical records and hospital information systems. Outpatient services included the number of visits to a gastroenterologist or IBD-nurse, scheduled phone consultations, and visits to the emergency department. Inpatient service was defined as the number of days hospitalised. Medication use for IBD was calculated using the mean number of daily dosages per type of drug used. Diagnostic procedures included the number and type of endoscopies and radiological procedures. Furthermore, the number and type of surgeries were retrieved. Information regarding the number of additional unscheduled phone consultations and e-mail contacts with the IBD-nurse was obtained from the 12-months follow-up questionnaire. For each of the abovementioned resource categories, the annual costs per patient were calculated by multiplying units of resource use by their unit costs¹⁶. For most healthcare resources, unit costs were available from the Dutch Guideline for Economic Evaluations in Healthcare and the Healthcare Insurance Board (supplementary table 1)^{17, 18, 19}. Unscheduled phone consultations and e-mail contacts with the nurses were charged as 15 minutes of their hourly wage¹⁷. Medication costs were calculated based on the individual dosage and their dose-prices (supplementary table 1)^{16, 19, 20}. Non-healthcare costs, i.e. transport and parking costs related to an outpatient visit, were calculated using standardised prices^{17, 19}. Finally, for patients using myIBDcoach an estimated annual license fee of €40 was added to their total direct healthcare costs. The total annual direct (healthcare and non-healthcare) costs per patient equaled the sum of all these cost-categories.

Indirect healthcare costs

To estimate the indirect healthcare costs only productivity loss because of sick leave for those with a paid job were included. A time horizon of one year would not provide reliable information on the effect of the intervention on work disability. Self-reported hours absence from work due to health problems were measured using the Work Productivity and Activity Impairment questionnaire (WPAI)²¹. Hours absent per week were extrapolated for the trial duration and multiplied by the average hourly Dutch wage retrieved from the Dutch Guideline for Economic Evaluations in Healthcare¹⁸.

Health utility

Changes in value of health over the 12-month study period were captured using the EuroQoL 5-dimensions (EQ-5D)²², filled out by all participants at baseline and at 12-months follow-up. The health utilities were computed using the Dutch tariffs for EQ-5D²³. The change in utility at 12 months compared to baseline equals the change in quality-adjusted life-years (QALYs).

Statistical analyses

Incremental costs, utilities, and cost-utility were assessed by the non-parametric bootstrapping method as recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) for cost-effectiveness analysis alongside trials²⁴. Between 3% (data derived from electronic medical records) and 26% (data derived from questionnaires) of observations contained missing values for costs or utilities. Preceding the bootstrap analyses, where 5,000 bootstrap replications were generated, these were replaced with estimates using stochastic imputation (SI). The variables medical centre (four centres), subtypes of inflammatory bowel disease (Crohn's disease or ulcerative colitis), treatment (no medication or mesalazine; immunosuppressive drugs; or biological therapy), age (numerical), sex (male or female), disease duration (numerical), disease activity at baseline (remission or active), smoking (non-smoker, active smoker, or ex-smoker), and educational level (five levels) were used as predictors in the SI model. All randomised patients were included in the analyses (intention-to-treat population). The results of the bootstrap iterations were presented in an incremental cost-utility ratio (iCUR) plane, an incremental net monetary benefit (iNMB) curve, and a cost-effectiveness acceptability curve (CEAC), representing the probability the intervention is cost-effective. The iNMB was calculated as $iNMB = \lambda * \Delta QALY - \Delta Cost$ where λ is the decision maker's maximum willingness to pay for a QALY. An iNMB above zero indicates the intervention generates monetary benefits at the chosen λ . In the Netherlands, a willingness-to-pay (WTP) threshold of €80,000 per QALY is used. As many bootstrapped iCUR replications indicated cost-savings but minor loss in QALY, we furthermore used a willingness-to-accept (WTA) threshold of €100,000 savings per QALY lost. A two-sided p-value ≤ 0.05 was defined as statistically significant. All statistical analyses were performed using SPSS version 22.0.

RESULTS

In total, 909 patients were included in the myIBDcoach study, of whom 465 were randomised to the intervention group and 444 to the control group. The baseline characteristics of the two study groups were similar and were representative for the general

IBD population in the Netherlands with regard to demographics and disease activity (table 1)²⁵. At the end of the 12-month study period, 27 patients (6%) in the intervention group and 1 patient (0.02%) in the control group were lost to follow-up. At baseline, 382 patients (82%) in the intervention group and 369 (83%) in the control group completed the paper questionnaires on healthcare utilisation, health-related quality of life, and work-productivity. At 12 months, these questionnaires were completed by 340 (73%) patients in the intervention group and 331 (75%) patients in the control group.

Direct and indirect annual costs and QALYs

The mean annual direct costs in the intervention group were €7,048 per patient compared to €7,423 per patient in the control group, while the mean indirect costs were €1,886 in the intervention group compared to €2,058 in the control group. This resulted in a mean annual cost saving of €547 per patient (95%CI €-1,029 to €2,143) favouring telemedicine. Table 2 shows averages of the main annual direct cost categories, sick leave costs, and of QALYs per year in the two treatment strategies. Within the direct healthcare costs, outpatient visits and drug costs were the main cost savers, responsible for an annual saving of €104 (95%CI €79 to €129) and €216 (95%CI €-776 to €1,209) respectively. Patients in the intervention group showed a mean gain in quality adjusted life years (QALY) of 0.002 (95%CI -0.022 to 0.018).

Table 1. Patient characteristics.

	MyIBDcoach (n=465)	Standard care (n=444)
Center, N		
Maastricht University Medical Center	133	131
Leiden University Medical Center	144	152
Zuyderland Medical Center Sittard	117	102
St. Antonius Hospital Nieuwegein	71	59
Gender, N (%)		
Male	194 (41.7)	180 (40.5)
Female	271 (58.3)	264 (59.5)
Age at diagnosis, mean (SD)	30.7 (13.5)	30.4 (13.6)
Age at inclusion, mean (SD)	44.0 (14.1)	44.1 (14.2)
Disease duration (years), mean (SD)	12.8 (10.4)	13.1 (10.8)
Phenotype, N (%)		
Crohn's disease	282 (60.6)	262 (59.0)
Ileal	87/282 (30.9)	68/262 (26.0)
Colonic	67/282 (23.8)	63/262 (24.0)
Ileocolonic	128/282 (45.4)	131/262 (50.0)
Upper gastrointestinal modifier	34/282 (12.1)	26/262 (9.9)
Nonpenetrating, nonstricturing	169/282 (59.9)	152/262 (58.0)
Stricturing	76/282 (27.0)	70/262 (26.7)
Penetrating	37/282 (13.1)	40/262 (15.3)
Perianal disease modifier	67/282 (23.8)	62/262 (23.7)

Table 1. Patient characteristics. (continued)

	MyIBDcoach (n=465)	Standard care (n=444)
Ulcerative colitis	183 (39.4)	182 (41.0)
Proctitis	26/183 (14.2)	27/182 (14.8)
Left sided	81/183 (44.3)	70/182 (38.5)
Pancolitis	76/183 (41.5)	85/182 (46.7)
Treatment, N (%)		
No medication/mesalazine	173/465 (37.2)	147/444 (33.1)
Immunosuppressives	122/465 (26.2)	131/444 (29.5)
Biologicals	170/465 (36.6)	166/444 (37.4)
Baseline disease activity, N (%)		
Remission	394/465 (84.7)	380/444 (85.6)
Active disease	71/465 (15.3)	64/444 (14.4)
Employment at baseline, N (%)	241/384 (62.7)	235/372 (63.2)
Work-productivity (WPAI; mean hours of productivity loss per study year, (SD))	54.3 (232.6)	59.1 (218.4)
Utility (EQ5D; mean score, (SD))	0.83 (0.15)	0.81 (0.17)

WPAI, work productivity and activity impairment; EQ5D, EuroQoL 5-dimensions; SD, standard deviation.

Table 2. Mean costs (in Euro) and QALY per patient in the two groups during the study period.

	Intervention group (SD)	Control group (SD)	Incremental (95% CI)
Direct healthcare costs	7,048 (8,458)	7,423 (8,522)	375 (-742, 1,501)
Non-drug healthcare costs	762 (2,412)	960 (2,386)	198 (-157, 554)
Drug costs	6,244 (7,487)	6,460 (7,757)	216 (-776, 1,209)
Out-of-pocket costs	2 (1.9)	3 (2.2)	1 (0.8, 1.3)
IBD-coach related	40	0	+40
Indirect healthcare costs	1,886 (8,084)	2,058 (7,587)	172 (-848, 1,192)
Total costs	8,934 (12,256)	9,481 (11,757)	547 (-1,029, 2,143)
QALY gains	0.034 (0.150)	0.032 (0.162)	0.0020 (-0.022, 0.018)

IBD, inflammatory bowel disease; QALY, quality-adjusted life year.

Incremental cost-effectiveness and uncertainty

The scatter plot of the iCURs resulting from the 5,000 bootstrapped replications for the imputed data set from a societal perspective is provided in figure 1 (for the cost-effectiveness planes from a healthcare perspective see supplemental figure 1 and 2). Using a WTP threshold of €80,000 and a WTA threshold of €100,000, the intervention was cost-effective in 83% of all replications. In only 6% of replications the intervention was accompanied by higher cost and lower health utility. At the Dutch cost-effectiveness threshold of €80,000 per QALY, the intervention has an iNMB of €707 per patient (95%CI -1,241 to 2,544) per year (figure 2). Figure 3 shows the uncertainty analyses of the iCUR and iNMB. While myIBDcoach dominates usual care even at a WTP threshold of € zero per QALY, some uncertainty remains and as there is no threshold at which myIBDcoach is 100% certain cost-effective.

Figure 1. Scatter plot of incremental mean cost against incremental mean QALYs of telemedicine compared to standard care. Each data point was obtained from one bootstrap.

Figure 2. Incremental net monetary benefit (iNMB) curve for telemedicine versus standard care.

Figure 3. Cost-effectiveness acceptability curve (CEAC) for telemedicine versus standard care.

DISCUSSION

In this cost-utility analysis regarding data from a pragmatic, randomised controlled trial, we showed that telemedicine with myIBDcoach was cost effective compared to standard care for IBD patients. Positive effects of telemedicine on IBD outcome have extensively been demonstrated. However, broad implementation is currently hindered as a result of lacking evidence on cost-effectiveness. To the best of our knowledge, this was the first complete economic evaluation of a telemedicine intervention versus standard care for IBD patients.

Telemedicine with myIBDcoach resulted in lower mean annual costs and a small mean gain in quality adjusted life years. At the Dutch threshold of €80,000 per QALY, the incremental net monetary benefit was €707 per patient per year. Benefits of telemedicine in IBD have been evaluated in two previous studies. The first trial, in which 333 patients in Denmark with mild-to-moderate UC treated with mesalazine were randomised to care via a telemedicine tool or standard care and followed for 12 months, showed that tight monitoring of disease activity and personalised treatment strategies resulted in cost savings of €189 per patient per year, mostly due to fewer outpatient visits²⁶. In addition, improvement in disease-specific quality of life was found. As quality of life was not measured by the EQ-5D, cost per QALY could not be calculated. Regarding indirect health-care costs, no statistically significant difference in number of work days lost through illness was observed between the two groups. The second study by the same group, a 12-month observational study in 92 (23 web-based care) CD patients, found lower direct

costs of €699 per patient per year when infliximab treatment was personally scheduled by web-administration, as compared to standard scheduled infliximab administration in the outpatient clinic²⁷. However, this web-based strategy did not show an improvement in quality of life nor a change in time missed from work due to CD²⁸. In line with our results, both studies showed that individualisation of disease management enabled by telemedicine was accompanied by a reduction of direct healthcare costs due to more efficient use of resources. Additionally, telemedicine can contribute to earlier identification of patients with insufficiently controlled disease who tend to be undertreated in current practice. Mounting evidence underscores that tight control of disease activity and optimisation of medication adherence prevents chronic uncontrolled mucosal inflammation, subsequent irreversible bowel damage, surgeries, and hospitalisation^{29,30,31}. By implementing such a strategy with telemedicine, flares can be detected earlier and the delay to treatment minimised. The abovementioned UC study indeed showed that implementation of guided self-management with personalised action plans by which patients could immediately self-initiate treatment in case of symptoms shortened flare duration²⁶. The combination of close monitoring and immediate intervention in case of a relapse might also have contributed to the reduction in hospitalisations in our study.

The cost savings in our study were mainly due to a reduction in outpatient visits and medication costs. We speculate that the latter might have been due to a reduction in flare duration and thereby a shortened therapy window. Additionally, timely optimisation of conventional therapy might prevent escalation to more expensive biologicals. Currently, several trials assess the possibilities for de-escalation of biological treatment in patients with sustained remission in order to improve safety and reduce healthcare costs. Proposed strategies include reducing dosage, increasing dosage intervals, or by discontinuation of biological therapy. Long-term studies are presently carried out to evaluate the safety, effects, and costs of these strategies^{32,33}. Telemedicine can add value to these strategies by closely monitoring disease activity and immediate re-escalation when indicated.

The main strength of this economic evaluation was that the data were obtained from a trial with a pragmatic randomised design, thus based on common daily practice. A large unselected heterogeneous group of patients, clinicians, and clinical practices were included to maximise the generalisability of the results to everyday practice. A possible limitation of this study was the lack of detailed information regarding laboratory tests as they were not systematically reported in medical records. However, these tests were previously found to account for a small proportion of the total costs and are therefore unlikely to have major impact on the reported results. Furthermore, as laboratory tests are regularly linked to outpatient visits, the total costs related to these tests are probably lower in the telemedicine group. In addition, some parameters were collected by questionnaires, resulting in possible selection bias. Yet, we found no statistically significant

differences in gender, age, phenotype, disease severity or educational level between patients who returned their questionnaires and those who did not. We calculated the indirect healthcare costs using the self-reported hours of sick leave from work over the past 7 days obtained from the WPAI and extrapolated these data for 1 year. This method could have under- or overestimated the total amount of indirect healthcare costs. However, in view of the large sample size and under the assumption that weekly sickness absence would occur at a constant rate throughout the observation period in each treatment group, the indirect costs estimated can be considered accurate. Additionally, we might have slightly overestimated the total net monetary benefit as we calculated a plain annual license fee of €40 per patient using telemedicine. These costs were based on the first version of myIBDcoach, without costs for implementation and without additional costs related to any potential healthcare reorganisation (e.g. extra hours work for an IBD-nurse). However, we expect that the additional actions related to myIBDcoach performed by the IBD-nurses, i.e. analysis of the monitoring module and subsequent actions, and answering to patients' messages, are at least partly compensated by the information and education function of the e-learning modules, which is normally a face-to-face task of the IBD-nurse.

Implementation telemedicine assists healthcare providers in delivering high-quality, and high-value care. For IBD, telemedicine furthermore enables gastroenterologists to implement a tight control strategy despite the currently overburdened outpatient clinics. We believe that broad implementation of telemedicine in parallel with reorganisation of care can improve long-term disease outcome and reduce healthcare costs. Additionally, interventions based on aberrant patient-reported values, such as smoking, an unfavourable nutritional status, or medication non-adherence, might contribute to better outcome. Furthermore, by systematic registering of PROMs and quality indicators, telemedicine can contribute to improving quality of care by benchmarking and evaluating practice variations. Lastly, shifting tasks from doctors to nurses, for example by telemonitoring of patients with a mild disease course or those in remission supervised by a specialised nurse, could further constrain costs.

Ameliorating quality of care for chronic diseases has been defined as improving patients' experience of care, improving long-term disease outcomes, creating a healthier population, and reducing costs of healthcare^{20, 34, 35}. Telemedicine with myIBDcoach has previously shown to improve patient experience of care and to improve disease outcomes^{14, 15}. The current study showed that implementation of telemedicine has an 83% chance to be cost-effective. Therefore, telemedicine may be a promising tool in restructuring IBD care towards more personalised, efficient and value-based healthcare.

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PART III

Chapter 7

Novel perceived stress and
life events precede flares of
inflammatory bowel disease:
a prospective 12-month follow-up study

Dion Wintjens, Marin de Jong, Andrea van der Meulen-de Jong,
Mariëlle Romberg-Camps, Marco Becx, Jeroen Maljaars,
Ad van Bodegraven, Nofel Mahmmod, Tineke Markus, Jeoffrey Haans,
Ad Masclee, Bjorn Winkens, Daisy Jonkers, Marieke Pierik

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ABSTRACT

Background: Inflammatory bowel disease (IBD) is characterised by recurrent disease flares. The impact of psychosocial wellbeing on the occurrence of flares is unclear. In this prospective study, we aimed to evaluate the association between patient-reported psychosocial wellbeing and disease flares using continuous monitoring.

Methods: Consecutive IBD patients were recruited from the myIBDcoach telemedicine study cohort. During 12 months, participants reported on disease activity and anxiety, depression, fatigue, perceived stress, and life events every one to three months. Flares were defined using a combination of clinical disease activity and additional measurements. Generalised estimating equation models were used to assess associations between psychosocial wellbeing and flares over time. The influences of both the presence of psychosocial symptoms in general and novel psychosocial symptoms were analysed.

Results: In total, 417 patients were included. Forty-nine patients (11.8%) experienced a flare during the study period. The occurrence of life events in the preceding three months was positively associated with flares (odds ratio [OR] 1.81; 95% confidence interval [CI] 1.04-3.17), while the presence of anxiety, depression, fatigue and perceived stress in general was not. However, novel perceived stress (OR 2.92; 95% CI 1.44-5.90) was associated with flares.

Conclusions: The occurrence of life events and novel perceived stress are associated with disease flares in the next three months, while the presence of perceived stress in general is not. These findings underline the importance of continuous personalised monitoring of IBD patients and may contribute to the prevention of disease flares.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a chronic and disabling disease characterised by recurrent periods of disease activity. These flares warrant escalation of medical treatment and often require hospitalisations or surgery. Recurrent flares may also lead to irreversible bowel damage and disease progression (e.g. the occurrence of complications like fistula and stenosis).^{1, 2} Although biochemical markers are available for early detection of disease activity³, identification of factors contributing to the emergence of flares might be an even more interesting approach to improve the outcome of IBD.

Regarding potentially flare-inducing factors, psychosocial wellbeing of patients is of interest. While not systematically monitored by healthcare professionals in routine care, a high prevalence of psychological disorders such as anxiety and depression is reported in the IBD population.^{4, 5} This may be a consequence of the chronic disease itself, but it is also hypothesised that impaired psychosocial wellbeing can negatively impact gut health through multiple immune-neuroendocrine brain-gut interaction pathways.^{6, 7}

A large number of studies have investigated the association between psychosocial wellbeing and disease activity in IBD, although many are limited by their cross-sectional design, thereby potentially neglecting the aforementioned bi-directionality of the brain-gut axis. When taking into account only the longitudinal studies, contradictory results have been reported regarding the effects of anxiety and depression on flares.⁸ Perceived stress and life events have been studied more extensively and it has been reported that a positive association exists between flares and perceived stress in most longitudinal studies.⁹⁻¹⁴ Though, in many studies, careful interpretation is advocated due to low sample size and the sole use of clinical disease activity indices to define flares, because these indices are poor predictors of mucosal inflammation.¹⁵ Also, perceived stress may affect intestinal motility and may magnify visceral sensitivity, leading to worsening of abdominal symptoms in the absence of inflammation.^{16, 17} It remains debatable to what extent mood disorders and perceived stress are associated with disease flares. Since, for instance, depression and perceived stress can both be present for longer periods^{13, 18}, it may be relevant to focus on within-subject changes in psychosocial wellbeing rather than to analyse only the presence of impaired psychosocial wellbeing preceding flares, which has, to our knowledge, not been done before.

Recently, de Jong et al. showed that continuous monitoring at home with the tele-medicine tool 'MyIBDcoach' is safe and even reduced outpatient visits and hospital admissions.¹⁹ MyIBDcoach continuously monitors patient-reported disease activity and psychosocial wellbeing through questionnaires. This method of data collection may provide important insights in psychosocial wellbeing over time. In this prospective

study, we aimed to evaluate which domains of psychosocial wellbeing, when impaired, were associated with future disease flares based on data from the myIBDcoach trial.

MATERIALS AND METHODS

Design and procedures

All data used in this study were derived from the myIBDcoach study cohort. The design of this randomised controlled telemedicine study has previously been described in detail.⁽¹⁹⁾ In short, IBD patients were included in four hospitals in the Netherlands (i.e. two academic hospitals, Maastricht University Medical Centre and Leiden University Medical Centre, and two regional hospitals, Zuyderland Medical Centre Sittard and St. Antonius Hospital Nieuwegein). Patients between 18 and 75 years of age who had a histopathologically corroborated diagnosis of IBD were eligible for inclusion. Exclusion criteria comprised insufficient knowledge of the Dutch language, lack of internet access by computer, tablet or smartphone, or a hospital admission within 2 weeks prior to inclusion. Also, patients with an ileoanal pouch or ileorectal anastomosis, or IBD unclassified (IBD-U) were excluded. After inclusion, patients were randomised in a 1:1 ratio to standard care (control group) or to care through myIBDcoach (intervention group) and followed for at least 12 months. The details of the telemedicine system myIBDcoach have been described elsewhere.⁽²⁰⁾ In brief myIBDcoach is a secured webpage which is accessible through computer, tablet or smartphone. The system provides monthly monitoring modules, including questions regarding disease activity, use of medication, treatment adherence, smoking status and psychosocial wellbeing. When patients achieved sustained remission (i.e. low clinical activity for three consecutive months), it was allowed to complete the monitoring module once every three months. When predefined thresholds, for instance on clinical disease activity, were exceeded, a health-care provider of the local team contacted the patient for further assessment. The study was approved by the Medical Research Ethics Committee of the Maastricht University Medical Centre+, being applicable to all participating centres. This trial was registered at ClinicalTrials.gov (NCT02173002).

For the present study, we included all patients who received care through myIBDcoach (i.e. the intervention arm of the randomised study). Patients without a single period of documented remission during follow-up were excluded since this period of remission was required to analyse the association between the development of disease flares and preceding psychosocial wellbeing. Detailed baseline data at the time of inclusion in MyIBDcoach (i.e. patient characteristics, disease phenotype, disease duration and previous treatments) were collected by scrutinising patient files using standardised registration forms. During the 12 months of follow-up, questionnaires on disease activ-

ity (MIAH-questionnaire²¹ and psychosocial wellbeing (i.e. anxiety, depression, fatigue, perceived stress, and life-events) were completed every 1-3 months.

Definitions

In line with previous analyses based on the myIBDcoach tool, flares were defined as clinical symptoms (i.e. positive score on the MIAH-questionnaire or symptoms during outpatient visits) indicative of disease activity in combination with at least one of the following: concurrent calprotectin >250 µg/g in the stool or active disease determined by endoscopy, magnetic resonance imaging or computed tomography. In daily practice, in case of clinically severe symptoms suggestive for IBD disease activity, the treating physician occasionally judged these symptoms to be evident enough to adjust therapy. Therefore, to capture all flares, also clinical episodes were defined as flares if symptoms suggestive of IBD disease activity resulted in a dose escalation or initiation of a new drug to induce remission. Psychosocial parameters were assessed through a patient-reported questionnaire containing one question for each psychosocial domain of interest (table 1). For anxiety, depression, and fatigue, questions were answered on a 5-point Likert-scale (i.e. 'seldom or never', 'occasionally', 'regularly', 'often', or 'always or almost always'). Cut-offs were determined based on the smallest Euclidian distances compared to validated questionnaires (i.e. HADS-A 22, HADS-D 22, and VVS23). The performance of the questionnaire is shown in table 1. For perceived stress, we used a VAS-scale on which a patient could report on their current stress level (range from 1 to 10) in which a higher score reflects higher stress levels. This scale showed a moderate though significant cor-

Table 1. Overview of psychosocial questionnaire used in the myIBDcoach telemedicine tool.

Domain	Question	Scale	Cut-off	Performance versus validated questionnaire (sens/spec)
Anxiety	In the past two weeks I ... felt anxious.	Likert (1-5)	2 (occasionally)	HADS-A ²⁴ (64/82)
Depression	In the past two weeks I ... felt miserable or depressed.	Likert (1-5)	3 (frequently)	HADS-D ²⁴ (73/93)
Fatigue	In the past two weeks I ... felt fatigue.	Likert (1-5)	3 (frequently)	VVV ²⁵ (90/100)
Perceived stress	Rate your current stress level on a scale from 1 to 10, what number would you give?	VAS (1-10)	NA	PSS ²⁶ (R = 0.654)
Life events	Did you experience any important or drastic events during the last period which influenced your feelings?	Dichotomous	NA	NA

VAS, visual analogue scale; NA, not applicable; sens, sensitivity; spec, specificity; HADS-D, Hospital Anxiety and Depression Scale – Depression; HADS-A, Hospital Anxiety and Depression Scale – Anxiety; VVV, Verkorte VermoeidheidVragenlijst (translated: Short Fatigue Questionnaire); PSS, Perceived Stress Scale

relation with the Cohen's Perceived Stress Scale (PSS; $r = 0.654$).⁽²⁴⁾ However, it should be noted that the PSS is based on perceived stress during the previous month, while our scale measures current stress levels. A cut-off point of 4, based on expert opinion of our team of gastroenterologists and our population's average, was used to differentiate low versus high perceived stress levels. The occurrence of life events was scored in a binary approach (i.e. yes/no). The underlying reason for the life event was answered as an open-end question and was therefore neglected in the analysis.

Statistical analysis

Baseline characteristics are presented as means with corresponding standard deviations (SD) for numerical variables with a normal distribution, as medians with corresponding interquartile ranges (IQR) for numerical variables without a normal distribution, and as number of patients (%) for categorical variables. For comparison between groups, the independent-samples t-test and Chisquare test or Fisher's exact test, when appropriate, were used for numerical and categorical variables, respectively.

Generalised estimating equations (GEE) models were used to identify associations between psychosocial wellbeing and the subsequent development of flares over time. This method is used to account for repeated measures within the same patient, where the covariance pattern was unstructured. Since it was unknown how long a patient was in remission when entering the study, the first three months of all patients were ignored in the analyses. Next, each month of follow-up was considered either as positive or negative with respect to flares, according to the aforementioned definition. Also, patient-reported psychosocial wellbeing was assessed with intervals of one month using the aforementioned cut-offs. When active disease was present at baseline or when a flare occurred during follow-up, the subsequent six months were excluded from the analysis to correct for a potential effect of disease activity and the subsequent remission-induction therapy on the psychosocial wellbeing of a patient. This can be considered as a wash-out period for both gastrointestinal inflammation and psychosocial imbalance caused by the preceding flare. Since patients could choose to fill in the questionnaires either once every month or once every three months, all models estimate the effect of psychosocial wellbeing on disease activity in the next quarter.

In the first GEE model, the association between flares and the presence of psychosocial symptoms in general was assessed. Predefined cut-offs were used to indicate the presence or absence of all psychosocial factors available in myIBDcoach, regardless of the prior psychosocial wellbeing of the patient. In the second GEE model, the association between flares and novel psychosocial symptoms was assessed. Here, differences in psychosocial parameters over time were determined to separate novel symptoms from pre-existing symptoms. At each time point the alteration in psychosocial parameters was regarded positive when this change exceeded the cut-off values of these

parameters (e.g. from 'seldom or never feeling depressed' (i.e. score 1) to 'often feeling depressed' (i.e. score 4)) in the three months preceding this time point. Life events were only analysed in the first model, since life events are 'novel' by definition and therefore the second model is not applicable. To ensure a prospective association between the psychosocial parameters and subsequent flares, psychosocial parameters were not taken into account as predictors when positive at the same time point as the flare. For example, when a patient experienced a flare between time point 5 and 6, the latter was regarded as 'time point of flare' and psychosocial scores from time point 3 to 5 were used in the model as explanatory variables.

All results were analysed using a multivariable model including gender, disease phenotype, disease duration at baseline, and smoking status at baseline to correct for their potential confounding effect on disease flares. Although our study was underpowered for additional confounders, medication use at baseline was added to the model as a sensitivity analysis. All analyses were conducted using a significance level of 0.05. Two-sided p -values ≤ 0.05 were considered as statistically significant.

RESULTS

In total, 465 patients were allocated to the myIBDcoach intervention.⁽¹⁹⁾ Of these, 9 never started using the application and 18 were lost to follow-up. After exclusion of these patients and patients with IBD-U ($n=3$), patients without any completed questionnaire ($n=11$), and patients without a single period of remission ($n=7$), 417 patients were eligible for this study. Of these, 49 patients (11.8%) developed a flare during follow-up (i.e. change from inactive to active disease). Two of these patients developed a second flare after remission was re-obtained. Flares were defined by clinical symptoms in combination with an elevated fecal calprotectin, active disease on endoscopy or imaging, and adjustment of therapy by a gastroenterologist in 14 (27.4%), 21 (41.2%), and 16 (31.4%) cases, respectively. Baseline characteristics of these patients (i.e. relapsers) compared to those not developing a flare during follow-up (i.e. non-relapsers) are presented in table 2. No significant differences in baseline characteristics were found between relapsers and non-relapsers, except for a greater proportion of smokers in the latter group ($p=0.005$). The average time from inclusion to their first disease flare for relapsers was 6.4 (SD = 2.6) months.

Regarding the presence of psychosocial symptoms in general, only the occurrence of life events (Odds ratio (OR) 1.81, 95% Confidence Interval (95%CI) 1.04-3.17) was associated with flare development in the next three months (table 3). Neither anxiety (OR 0.73, 95%CI 0.38-1.39), nor depression (OR 1.33, 95%CI 0.70-2.55), nor fatigue (OR 1.91, 95%CI 0.98-3.73), and perceived stress (OR 1.09, 95%CI 0.62-1.91) were statistically significantly

Table 2. Baseline characteristics, stratified by occurrence of disease flares.

	Relapsers (n=49)	Non-relapsers (n=368)	p-value
Crohn's disease n (%)	26 (53.1)	222 (60.3)	0.331
Male, n (%)	15 (30.6)	158 (42.9)	0.100
Montreal at diagnosis [^]			
Age (CD & UC)			0.600
A1, n (%)	8 (16.3)	60 (16.3)	
A2, n (%)	26 (53.1)	219 (59.5)	
A3, n (%)	15 (30.6)	89 (24.2)	
Disease location (CD)			0.741
L1, n (%)	7 (26.9)	73 (32.9)	
L2, n (%)	6 (23.1)	55 (24.8)	
L3, n (%)	13 (50.0)	94 (42.3)	
Disease behavior (CD)			0.958
B1 (CD), n (%)	16 (61.5)	134 (60.6)	
B2 (CD), n (%)	7 (26.9)	57 (25.8)	
B3 (CD), n (%)	3 (11.5)	30 (13.6)	
Disease extent (UC)			0.768
E1 (UC), n (%)	2 (8.7)	19 (12.8)	
E2 (UC), n (%)	10 (43.5)	69 (46.3)	
E3 (UC), n (%)	11 (47.8)	61 (40.9)	
Age at baseline (years), mean (SD)	46.08 (15.24)	43.95 (13.71)	0.313
Disease duration at baseline (years), mean (SD)	13.45 (10.93)	13.39 (10.40)	0.971
Active disease at baseline, n (%)	4 (7.7)	28 (8.2)	0.908
Medication use at baseline			0.434
No medication/5-ASA, n (%)	15 (30.6)	142 (39.3)	
Immunomodulators, n (%)	16 (32.7)	93 (25.8)	
Biologics, n (%)	18 (36.7)	126 (34.9)	
Current smoking at baseline, n (%)	1 (2.0)	65 (17.7)	0.005*
History of IBD-related surgery at baseline, n (%)	5 (16.7)	41 (23.3)	0.420

N, number of patients; CD, Crohn's disease; UC, Ulcerative colitis; SD, standard deviation; 5-ASA, 5-aminosalicylic acid; *, p-value below 0.05; ^, classification according to Montreal Classification.³⁹ Age was defined as below 17 (A1), between 17 and 40 (A2) and above 40 (A3). Disease location of CD was defined as ileal involvement (L1), exclusive colonic involvement (L2), ileocolonic involvement (L3). Disease behaviour of CD was defined as non-stricturing/non-penetrating (B1), stricturing (B2), penetrating (B3). Disease extent of UC was defined as ulcerative proctitis (E1), left sided UC (E2) and extensive UC (E3).

associated with flare development. Regarding novel psychosocial symptoms (i.e. alteration exceeding cut-off), only perceived stress (OR 2.92, 95%CI 1.44-5.90) was associated with subsequent flares (table 3), independent of the presence of other psychosocial factors in general. No statistically significant association with subsequent flares was found in this second GEE model for anxiety (OR 1.12, 95%CI 0.50-2.51), depression (OR 1.28,

95%CI 0.54-3.07), and fatigue (OR 1.58, 95%CI 0.79-3.15). All results were adjusted for gender, disease phenotype, disease duration, and smoking status. When results were analysed for CD and UC separately, the association between flares and both life events and perceived stress tended to be stronger in CD. However, due to the small number of relapses, the study was not powered to analyse these associations and the results should be interpreted with care.

In a first sensitivity analysis, medication use at baseline was added to the model. By applying this, all results remained similar. As a second sensitivity analysis, different cut-offs of the questions regarding depression, anxiety, fatigue, and perceived stress were used. For depression, anxiety, and fatigue, both higher and lower cut-offs did not change the results. For novel perceived stress, a difference was observed. In case cut-offs higher than 4 were chosen, perceived stress was not statistically significant anymore (cut-off 5: OR 1.52, 95%CI 0.67-3.45), while cut-offs below 4 remained statistically significant (cut-off 3: OR 2.24, 95%CI 1.02-4.90).

Table 3. Association between both the presence of psychosocial symptoms in general (GEE model 1) and novel psychosocial symptoms (GEE model 2) and disease flares.

	GEE model 1: presence of psychosocial symptoms in general		GEE model 2: novel psychosocial symptoms only	
	OR	95%-CI	OR	95%-CI
Anxiety	0.73	0.38-1.39	1.12	0.50-2.51
Depression	1.33	0.70-2.55	1.28	0.54-3.07
Fatigue	1.91	0.98-3.73	1.58	0.79-3.15
Perceived stress	1.09	0.62-1.91	2.92	1.44-5.90**
Life events	1.81	1.04-3.17*	NA	NA

OR, Odds ratio; 95%-CI, 95%-Confidence Interval; *, p-value below 0.05; **, p-value below 0.01 All analyses were adjusted for gender, disease phenotype, disease duration at baseline, and smoking status at baseline.

DISCUSSION

In this prospective continuous telemedicine monitoring study we evaluated the effect of psychosocial wellbeing on subsequent disease flares. A positive association was found between both life events as well as perceived stress and disease flares. We hereby identified a relevant difference between the presence of perceived stress in general, irrespective of changes over time, and novel perceived stress. Only the latter was prospectively associated with occurrence of disease flares in the next three months. Anxiety, depression and fatigue were not associated with disease flares.

The observed association between disease activity and perceived stress has previously been described. However, the power of many studies was limited due to methodological flaws such as cross sectional analyses, small sample size, and the lack of

objective measurements of disease activity.⁽²⁵⁾ Since IBD patients often experience IBS-like complaints, the sole use of clinical disease activity indices to define flares may give an overestimation of relapses and therefore additional markers of inflammation are needed. So far, only a limited number of longitudinal studies have used a combination of symptoms and additional measurements (e.g. calprotectin or endoscopy) to define flares.^{11, 13, 14, 26} In a longitudinal study using combined a clinical disease activity index and fecal calprotectin concentration, short-term perceived stress was positively associated with subsequent IBD symptoms, but not with 'objectively' assessed inflammation by fecal calprotectin measurement.⁽¹³⁾ These findings may explain some contradictory results from earlier studies and support our findings concerning the absence of an association between the presence of perceived stress in general and flares. Nonetheless, a difference between the presence of perceived stress in general and novel perceived stress was currently observed. In many studies, 'short-term' perceived stress has been analysed by using a questionnaire comprising the past month (e.g. Cohen Perceived Stress Scale²⁴ or Perceived Stress Questionnaire²⁷). Unfortunately, these questionnaires are insensitive for perceived stress in the period prior to this month. Therefore, exposure time to perceived stress is unknown and both 'novel' and 'longer lasting' stress are measured. To analyse the effect of intra-individual changes of perceived stress over time, longitudinal follow-up of both the outcome variable (i.e. disease flares) and perceived stress is necessary. To our knowledge, in only a few studies, both variables were repeatedly measured during follow-up.^{9-13, 26} Of these, none used the repetitive assessments to differentiate novel perceived stress from chronic or pre-existing perceived stress.

In the present study, we observed a clear difference between the effect of perceived stress in general and the effect of novel perceived stress. In healthy individuals, both internal and well as external stressors are in balance with behavioral and physiologic adaptive responses. Perceived stress may become detrimental when this balance is disturbed (e.g. via acute stressors).⁽²⁸⁾ It is hypothesised that perceived stress may affect the brain-gut axis through (I) activation of the hypothalamic-pituitary-adrenal axis and subsequent release of corticotropin releasing factor and cortisol, which have direct and indirect gastrointestinal immunostimulatory effects, (II) decreased activity of the vagal nerve and thereby a decreased anti-inflammatory effect, (III) increased activation of the sympathetic nervous system and subsequent increase of inflammatory cytokines, activation of the NF- κ B pathway, and activation of mast cells, and (IV) peripheral release of substance P by the enteric nervous system, acting as an inflammatory cytokine and stimulator of mast cells.^{6, 16} It is hypothesised that after such disturbance, homeostasis usually returns in most individuals.²⁸ Therefore it may be put forward that during prolonged stress, individuals can adapt to this new situation. This might explain why, in our study, only novel perceived stress was associated with flares. Though, another longitudinal study observed long-term perceived stress (i.e. covering two years prior to

measurement) to be associated with flares in the following 8 months, while short-term perceived stress (i.e. covering the month prior to measurement) was not.²⁶ However, their explanation of a proposed lengthy time scale for the evolution of effects of stress on the intestines was primarily based on animal studies. Coping strategies and consequent adaptation to chronic stress may be different in humans. It is hypothesised that chronic stress enhances the effects of acute stress through greater and more prolonged increases in sympathetic activation following a stressor although supporting evidence is scarce.¹⁶ Future studies regarding perceived stress and disease flares, using the same methodology as the present study, should be performed to validate our findings.

The occurrence of life events was also associated with the development of a flare in the next three months. The most frequently answered type of life events were work-related (19.4%; e.g. dismissal or reorganisation), personal health issues (10.9%), to move house or renovate a house (10.9%), or the death of relatives or good friends (9.1%). The effect of life events on future disease activity is smaller when compared to perceived stress. Although life events by definition are correlated with perceived stress, the way of coping will determine whether the life event as a stressor leads to more perceived stress or not. We speculate that only patients with insufficient coping strategies will experience an increase in perceived stress. Unfortunately, our study is not designed to analyse these effects. Though, this hypothesis is supported by findings of another prospective study in which a combination of low stress and a good coping strategy was associated with the lowest risk of a disease flares.¹² Debate remains as contradictory results on the influence of life events have been reported by others, possibly due to differences in study design and methodology.^{8, 29}

In this study, no association was found between anxiety, depression or fatigue and subsequent disease flares. Anxiety and depression as comorbidities have extensively been studied in IBD patients and in a recent systematic review it has been shown that the prevalence rate of anxiety (20%) and depression (15%) is high in IBD compared to prevalence rates in the general population (7.3% and 3.2%, respectively).^{5, 30, 31} Though, a meta-analysis of prospective studies on the impact of a depressive state on disease activity showed no statistically significant association, which is in line with our study.³² The association between both anxiety and disease flares as well as fatigue and disease flares has not very frequently been studied. Anxiety seemed not to be associated, as in our study, with disease flares.^{11, 12, 33} Although longitudinal evidence for an association between fatigue and flares is lacking, a high prevalence of fatigue in active IBD has been observed.³⁴ In our study, this association could not be confirmed.

The strength of this study is the systematic and continuous monitoring of both disease activity and psychosocial wellbeing over a 12-month period in a large study population. Additionally, we were able to analyse within-subject changes of psychosocial wellbeing. Also, we defined disease flares using a combination of clinical disease activity (i.e. MIAH-

questionnaire) and additional parameters (i.e. fecal calprotectin, imaging or outpatient clinic visit with treatment adjustment). Some limitations also need to be addressed. First and most importantly, we did not use validated questionnaires for psychosocial wellbeing in the telemedicine tool. The questionnaires in MyIBDcoach were designed to screen for several relevant aspects potentially associated with patients' wellbeing and these questionnaires had to be concise for repeated use in a daily clinical practice setting. We therefore chose to apply only one 'screening' question per domain to limit loss of adherence. Though, previous studies have shown that single-question questionnaires can correlate well with comprehensive questionnaires (e.g. for perceived stress³⁵). Second, we were not able to obtain reliable data on the use of NSAIDs, the use of antibiotics or incident infections from the myIBDcoach tool, while several studies suggest that these variables are associated with disease flares.²⁹ On the other hand, a large longitudinal population-based study showed no effect of either of these variables and therefore we believe that the potential confounding effect, if present, is only minimal.⁹

Currently, we believe that the merit of psychosocial wellbeing in IBD patients is underestimated and hardly routinely assessed in daily practice. In this study, we addressed that special attention should be paid to novel perceived stress and life events and our data underline a possible need for tight psychosocial monitoring of IBD patients. Our findings concerning the association between novel perceived stress and disease flares need confirmation by future studies and such studies should take coping strategies into account. Eventually, personalised interventions in those who are at risk to develop flares is worth looking further into.

In conclusion, occurrence of recent life events and novel perceived stress were prospectively associated with the incidence of IBD disease flares in the next three months, while the presence of perceived stress in general is not. Also, no association was found between disease flares and anxiety, depression, or fatigue. This study underlines the importance of continuous personalised monitoring of IBD patients and may contribute to the prevention of disease flares.

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Chapter 8

Risk of impaired nutritional status and flare occurrence in IBD outpatients.

Corinne Spooren, Dion Wintjens, Marin de Jong,
Andrea van der Meulen-de Jong, Mariëlle Romberg-Camps,
Marco Becx, Jeroen Maljaars, Ad van Bodegraven, Nofel Mahmmoud,
Tineke Markus, Wim Hameeteman, Ad Masclee, Bjorn Winkens,
Daisy Jonkers, Marieke Pierik

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ABSTRACT

Background: Inflammatory bowel disease (IBD) patients are at risk of an impaired nutritional status. The impact thereof on the IBD relapse risk is clinically relevant, though sparsely investigated. Our aim was to explore the association between the risk of an impaired nutritional status and the occurrence of disease flares in IBD outpatients participating in a longitudinal telemedicine study.

Methods: IBD outpatients were recruited from the myIBDcoach study cohort, with one year clinical follow-up. Through myIBDcoach, a telemedicine tool, patients reported every 1-3 months on disease activity and risk of impaired nutritional status (i.e. Short Nutritional Assessment Questionnaire >1 and/or BMI <18.5 kg/m²). Data were analysed by generalised estimating equation modelling.

Results: In total, 417 patients were included. During follow-up, 49 patients (11.8%) flared after initial clinical remission and 53 patients (12.7%) showed an increased risk of an impaired nutritional status. The risk of an impaired nutritional status was associated with flare occurrence (OR 2.61 (95% CI 1.02-6.69)).

Conclusions: The risk of an impaired nutritional status was associated with subsequent flares in IBD outpatients. This emphasises the importance of monitoring disease activity in IBD patients at risk of an impaired nutritional status.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory disease of the gastrointestinal tract with Crohn's disease (CD) and ulcerative colitis (UC) as main subtypes. The disease course is characterised by a wide variation between patients in duration and frequency of relapsing and quiescent periods. Several factors have been associated with relapse risk, such as a high frequency of flares within the first year of diagnosis^{1,2}, poor medication adherence³, and active smoking in CD patients.⁴ However, these do not sufficiently predict the disease course. Identification of further factors contributing to the development of relapses is therefore warranted.

IBD patients are at risk of an impaired nutritional status due to disease-related changes in absorption and/or requirements, often in combination with an unbalanced dietary intake.⁵ Reported prevalences range from 16-75% in IBD patients.⁶⁻⁸ The variation may be due to heterogeneity in study methods and definitions used for defining an impaired nutritional status, in many publications often referred to as malnutrition. Defining malnutrition remains challenging. Therefore, the American Society of Parenteral and Enteral Nutrition (ASPEN) <https://www.nutritioncare.org/> recommends diagnostic characteristics to identify malnutrition in adults, by which two of the following six criteria need to be fulfilled: i.e. low energy intake, weight loss, loss of muscle mass, loss of subcutaneous fat, fluid accumulation, and handgrip strength.⁹ However, validated screening tools to identify patients at risk of malnutrition, such as the Short Nutritional Assessment Questionnaire (SNAQ) and the Malnutrition Universal Screening Tool (MUST) are more often used, since these are less time consuming.¹⁰

An impaired nutritional status may impact disease course. Malnutrition, defined by the Subjective Global Assessment which is a nutritional assessment instrument, has been found to be related to a diminished quality of life in hospitalised patients with IBD¹¹, and radiological assessed loss of muscle mass was associated with an increased risk of intestinal resection and postoperative complications in IBD patients.¹²⁻¹⁵ Furthermore, higher disease activity was associated with a lower skeletal muscle index among UC patients.¹³ In previous cross-sectional and longitudinal studies active disease was reported to affect body composition in both CD and UC patients.^{16,17} However, both CD and UC patients with quiescent disease can also suffer from an altered body composition (i.e. fat mass and fat free mass)^{18,19} and in a previous study the nutritional status of recently diagnosed IBD patients was already affected negatively.²⁰ So it can be hypothesised that the development of an impaired nutritional status could be a risk factor for the development of disease activity. Therefore, as an explorative study, we aimed to analyse whether the risk of an impaired nutritional status was associated with flare occurrence in quiescent IBD outpatients in a longitudinal, observational study.

MATERIALS AND METHODS

Study Design

For the present longitudinal study, available data from the myIBDcoach study were used in an explorative analysis. MyIBDcoach is a telemedicine tool, accessible on a secured webpage through computer, tablet or smartphone, for monitoring of IBD patients at home.²¹ In the myIBDcoach trial, the effect of disease monitoring with myIBDcoach on healthcare utilisation and quality of care was investigated. All consecutive IBD patients between 18-75 years, with sufficient knowledge of the Dutch language and internet access, from two tertiary referral centres and two non-academic hospitals in the Netherlands were eligible for inclusion for this trial and randomised in the myIBDcoach or standard care group. All patients had an established diagnosis of CD or UC, fulfilling the international diagnostic criteria.²²

Every single month patients in the telemedicine arm completed monitoring modules, including questions on e.g. disease activity, use of medication, smoking status, weight, and malnutrition risk based on the SNAQ. When a patient achieved remission (i.e. low clinical activity for three consecutive months) patients were allowed to complete the monitoring module once every three months. The study design is described in detail elsewhere.²³

The myIBDcoach study was approved by the Medical Research Ethics Committee of the Maastricht University Medical Centre+ (NL47697.068.14) and registered at ClinicalTrials.gov (NCT02173002) and the study protocol conformed to the provisions of the declaration of Helsinki. All patients gave written informed consent prior to participation.^{21, 23}

Patients who were randomised to the myIBDcoach intervention group were included in the present study. Baseline characteristics (e.g. height, disease phenotype, duration, and medication use) were extracted from patient files using standardised registration forms. During the 12 months of follow-up, every 1-3 months information on weight (to determine BMI), disease activity by a symptom-based patient-reported outcome measure (the Monitor IBD At Home (MIAH) questionnaire²⁴), and risk for malnutrition (by the SNAQ) was obtained.

In line with the myIBDcoach trial, flares were defined as clinical symptoms indicative of disease activity (MIAH) in combination with either a fecal calprotectin >250 µg/g, disease activity on endoscopy, magnetic resonance imaging or computed tomography, or dose escalation or initiation of a new drug to induce remission.²¹

The SNAQ is developed as a non-invasive screening tool to assess malnutrition in both in- and outpatient setting^{25, 26} and comprises 3 questions, i.e. unintentional weight loss over a predefined time period (depending on weight loss 2 or 3 points), experience of decreased appetite during the last month (1 point), and/or use of supplemental drinks or tube feeding during the last month (1 point). For the present study, the risk of

an impaired nutritional status was defined as a SNAQ ≥ 2 points and/or BMI < 18.5 kg/m². Both parameters were determined every 1-3 months.

Statistical Analysis

Numerical variables were presented as means with corresponding standard deviation (SD) and categorical variables as numbers with percentages. Baseline characteristics were compared between groups (patients who relapse versus who do not relapse) by the independent-samples t-test for numerical variables, and Chi-square test or Fisher's exact test when appropriate, for categorical variables. Generalised estimating equations model was used to identify an association between the risk of an impaired nutritional status and the development of flares in the following three months. This method accounts for repeated measures within the same patient, with an unstructured covariance pattern.

At each time-point of measurement, the flare status (yes/no) as well as the risk of an impaired nutritional status (yes/no) was recorded. In patients with quiescent disease, the first three months were excluded from the analyses to prevent potential carry-over effects of histological inflammation in clinical inactive patients at time of inclusion. When active disease was present at inclusion or during follow up, the following six months were excluded from the analyses as a wash-out period and to start the follow-up from a remissive state onwards.

For the generalised estimating equations model, all positive values on the risk of an impaired nutritional status in the three months preceding a flare were regarded as possible predictors.

Since we aimed to assess the prospective association, the risk of an impaired nutritional status measured at the same measurement moment as a flare was not considered as a predictor. Since patients were able to complete the questionnaires either every one or three months, the flare status was determined for the subsequent three months after the risk of an impaired nutritional status was assessed. The generalised estimating equations model was adjusted for potential confounding effects of sex, disease phenotype, disease duration at inclusion, and smoking status at inclusion. Two-sided P-values ≤ 0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS statistics for Windows, Version 22 (IBM, Armonk, NY).

RESULTS

In total, 465 IBD patients were allocated to the intervention group in the myIBDcoach trial.²¹ Patients who were not eligible, i.e. never started using the application, never

achieved a period of remission or were lost to follow-up for other reasons were excluded from further analyses. Finally, 417 patients were included in the present study.

Baseline characteristics at inclusion, stratified by flare status during follow up, are presented in table 1. During follow-up, 49 (11.8%) individual patients (CD=26, UC=23) experienced a flare after initial remission. There were fewer active smokers at inclusion among those that relapsed during follow-up compared to the 'non-relapsers' ($p=0.005$). There were no other differences in baseline characteristics between these groups.

Table 1. Patient characteristics, stratified by occurrence of disease flares.

	Relapsers (n=49)	Non-relapsers (n=368)	p-value
Crohn's disease n (%)	26 (53.1)	222 (60.3)	0.331
Male, n (%)	15 (30.6)	158 (42.9)	0.100
BMI (kg/m ²), mean (SD)	25.37 (4.3)	25.14 (4.0)	0.705
Montreal at diagnosis*			
Age (CD & UC)			0.600
A1, <17 years, n (%)	8 (16.3)	60 (16.3)	
A2, 17-40 years, n (%)	26 (53.1)	219 (59.5)	
A3, >40 years, n (%)	15 (30.6)	89 (24.2)	
Disease location (CD)			0.741
L1, ileal, n (%)	7 (26.9)	73 (32.9)	
L2, colonic, n (%)	6 (23.1)	55 (24.8)	
L3, ileocolonic, n (%)	13 (50.0)	94 (42.3)	
Disease behaviour (CD)			0.958
B1, non-stricturing non-penetrating, n (%)	16 (61.5)	134 (60.6)	
B2, stricturing, n (%)	7 (26.9)	57 (25.8)	
B3, penetrating, n (%)	3 (11.5)	30 (13.6)	
Disease extent (UC)			0.768
E1, proctitis, n (%)	2 (8.7)	19 (12.8)	
E2, left-sided, n (%)	10 (43.5)	69 (46.3)	
E3, pancolitis, n (%)	11 (47.8)	61 (40.9)	
Age at inclusion (years), mean (SD)	46.08 (15.2)	43.95 (13.7)	0.313
Disease duration at inclusion (years), mean (SD)	13.45 (10.9)	13.39 (10.4)	0.971
Active disease at inclusion, n (%)	4 (7.7)	28 (8.2)	0.908
Medication use at inclusion			0.434
No medication/5-ASA, n (%)	15 (30.6)	142 (39.3)	
Immunomodulators, n (%)	16 (32.7)	93 (25.8)	
Biologics, n (%)	18 (36.7)	126 (34.9)	
Current smoking at inclusion, n (%)	1 (2.0)	65 (17.7)	0.005 [^]

n, number of patients; SD, standard deviation; BMI, body mass index; 5-ASA, 5-aminosalicylic acid; SNAQ, Short Nutritional Assessment Questionnaire; [^], p-value below 0.05; *, classification according to Montreal Classification.⁴⁴; #, different patients

At inclusion, six (1.4%) patients had a BMI <18.5 kg/m², 216 (51.8%) patients had a BMI of 18.5-25 kg/m², 147 (35.3%) patients had a BMI of 25-30 kg/m², and 48 (11.5%) patients had a BMI >30 kg/m². In total, 53 (12.7%) individual IBD patients were at risk of an impaired nutritional status based on a positive SNAQ score (n=45), BMI <18.5 kg/m² (n=5), or both (n=3) during follow-up.

In the generalised estimating equations analyses, the risk of an impaired nutritional status was found to be associated with the occurrence of a flare in the following three months (OR 2.61 (95% CI 1.02-6.69, p=0.046)). Furthermore, in this model also female sex (OR 2.12 (95% CI 1.08-4.15, p=0.029)) was identified as a risk factor for the development of a flare, while active smoking showed a negative association (OR 0.14 (95% CI 0.02-0.97, p=0.047)) (table 2). In the generalised estimating equations model, medication use at time of inclusion was not incorporated as confounder due to the small number of relapsing patients during follow up. When medication use at time of inclusion was added to the model for IBD patients, a comparable increased risk was found (OR 2.48 (95% CI 0.96-6.41, p=0.061)), though not significant.

Table 2. Multivariable generalised estimating equations model: association between impaired nutritional status risk in IBD and disease flares.

	OR	95%CI	p-value
Impaired nutritional status	2.61	1.02-6.69	0.046 ^b
UC phenotype	1.43	0.78-2.65	0.251
Sex, female	2.12	1.08-4.148	0.029 ^b
Active smoker ^a	0.14	0.02-0.97	0.047 ^b ^
Disease duration ^a	1.01	0.98-1.04	0.642

OR, Odds ratio; 95%CI, 95% Confidence Interval; ^a, at inclusion; ^b, p-value below 0.05.

DISCUSSION

In this longitudinal study in daily practice, the risk of an impaired nutritional status, defined by a positive SNAQ or BMI <18.5 kg/m², was found to be associated with the occurrence of a flare.

Previous studies reported that a decreased skeletal muscle index increases the risk of an intestinal resection in hospitalised CD with an exacerbation¹², increases the need for colectomy in UC patients¹³, predicts the need for rescue therapy in acute severe UC patients²⁷, is associated with postoperative complications in IBD patients^{14, 15}, and is associated with anti-TNF treatment failure in IBD patients.²⁸ Furthermore, active disease affects body composition in both CD and UC patients, as found in previous cross-sectional as well as longitudinal studies.^{16, 17} However, to our knowledge, the current study is the first specifically analysing the association of impaired nutritional status risk

on flare occurrence. An impaired nutritional status may contribute to the development of a flare by malnutrition-induced changes in the immune system, by the altered cytokines (interleukin-6 and tumour necrosis factor- α), hormones (leptin), and/or increased intestinal permeability.²⁹⁻³² A mice study on the effects of fasting showed that changes in immune response occur rather early after inducing nutritional deficiency.³⁰

In the present study, the SNAQ in combination with BMI was used as screening method for risk of an impaired nutritional status, since the SNAQ alone may lead to underreporting in an outpatient setting.³³ The SNAQ and MUST both contain questions on unintentional weight loss and food intake. In contrast to the SNAQ, a low BMI (18.5-20 or <18.5 kg/m²) is taken into account in the MUST questionnaire. The MUST may however lead to overreporting of patients at risk in the outpatient setting.³³ Therefore, in line with one of the diagnostic criteria for malnutrition by the European Society for Clinical Nutrition and Metabolism (ESPEN)¹⁰, only a BMI <18.5 kg/m² was added to the SNAQ to capture all patients at risk for an impaired nutritional status in the current study. Fifty-three patients were at risk of an impaired nutritional status during follow up, of which the majority of the patients (n=45) had a positive SNAQ and BMI >18.5 kg/m², five patients had a BMI <18.5 kg/m² and negative SNAQ, and three patients had both a positive SNAQ score and BMI <18.5 kg/m².

The overall distribution of our patients over the different weight categories (according to the World Health Organization definitions)³⁴ were comparable with percentages of overweight and obesity in a representative healthy population in South Limburg, a province in the Netherlands.³⁵ The majority of the IBD patients in the present study had a normal BMI (51.8%) and a significant proportion was overweight (35.3%) or obese (11.5%). Due to an unfavourable fat-muscle ratio, which is not necessarily reflected by BMI, it cannot be excluded that patients with a BMI 18.5-25 kg/m² do not have a decreased muscle mass and are thereby being at risk of an impaired nutritional status.

A commonly used model for analysing the body composition is the two-compartment model in which body weight is subdivided in fat mass and fat free mass. Skeletal muscle mass represents a large proportion of the fat free mass. Prior studies reported that changes in fat free mass, are not always captured by malnutrition screening questionnaires in IBD patients.^{19, 36} This underlines the necessity in future studies to combine a malnutrition screening questionnaire with a simple, non-invasive body composition analysis, and also, to incorporate changes in fat free mass for timely identification of patients at risk. A technique which can be considered is the handgrip strength, as parameter of muscle strength.³⁷

In the present study, flare development was also found to be positively associated with female sex, and negatively with smoking status at inclusion. In CD for example, smoking is found to increase the risk of a flare, whereas in UC smoking cessation is.³⁸ Our finding may be affected by analysis of the total IBD population. Separate analyses

for CD and UC were not performed due to the limited sample size, but should be taken into account in future studies.

A major strength of the present study is the longitudinal design of the study in a relatively large, unselected outpatient study population. The study population was found to be representative for the general IBD population in the South Limburg area.^{21,39} Furthermore, by the use of telemedicine, disease activity, and malnutrition screening risk were measured repeatedly and standardised. Though, some limitations of this study should be addressed. For the present explorative study, available data from the myIBDcoach study were used. Therefore, no sample size calculation has been performed and we were not able to correct for all potential confounders for flare development, such as prior surgery, time since last flare, and prior smoking status. The present study shows a significant association between impaired nutritional status risk and flare occurrences in the entire IBD cohort. Separate analyses for CD and UC were not performed due to small numbers of patients. However, these analyses are of interest since factors influencing flare occurrence may differ between these phenotypes, and should be included in future studies. Furthermore, ongoing histological inflammation at inclusion and during follow up cannot be completely excluded since disease activity was monitored by clinical parameters. However, to prevent carry-over effects of histological inflammation, the first three months from patients with quiescent disease were excluded from the analyses. Finally, it should be taken into account that flares can be affected by enteral nutrition, particularly in CD.⁴⁰ However, in the present study, use of enteral nutrition was limited and was not found to impact our findings (data not shown).

The aim of the present explorative study was to investigate an association between the risk of an impaired nutritional status and flare occurrence. In clinical practice, it has already been shown that early treatment of malnourished inpatients for any disease or operation, based on screening, leads to a shorter length of hospital stay and is cost-effective.⁴¹ Since this is the first longitudinal study analysing the association of impaired nutritional status risk on flare occurrences, our results should be confirmed in other cohorts. Larger longitudinal studies on the impact of an impaired nutritional status risk, incorporating body composition analysis and muscle strength, and taking confounders and separate analysis for CD and UC into account, are of special interest to confirm the actual effect on disease activity. Additionally, studies on timely dietary and/or physiotherapy interventions, aiming to improve nutritional status and treatment outcome are warranted.

In conclusion, in the present longitudinal observational study, we found an association between the presence of the risk of an impaired nutritional status and IBD flare occurrence. This emphasises the importance of monitoring disease activity in IBD patients at risk of an impaired nutritional status.

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Chapter 9

Exploring conditions for redistribution of anti-TNFs to reduce spillage. A study on the quality of anti-TNF home storage.

Marin de Jong, Marieke Pierik, Andy Peters, Mark Roemers,
Veronique Hilhorst, Astrid van Tubergen

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ABSTRACT

Background: Biologicals are potent drugs for immune mediated inflammatory diseases (IMIDs). After discontinuation or switch of therapy, many patients have unused biological injectors left. We aimed to evaluate potential redistribution of unused injectors to prevent spillage of these costly drugs by assessing 1) the quality of transport and home storage through the proportion of injectors stored within the recommended temperature range (2°C-8°C) and 2) acceptance of redistribution by patients.

Methods: All golimumab users, irrespective of the indication, at Maastricht University Medical Centre were eligible for inclusion. Patients received golimumab in a sealed bag containing a validated temperature sensor, measuring temperature every 5 minutes. Patients were asked to store their medication as usual. Deviations from the recommended range were defined as any duration below 0°C and >30 minutes below 2°C or above 8°C. After 3 months, patients completed a questionnaire on their opinion towards potential redistribution of unused biologicals.

Results: Fifty patients (42.0% male, mean age 53.2±14.3 years) received 276 injectors. The mean storage time was 30.9±33.1 days. Only 11.6% of the injectors were stored within the recommended temperature range. In addition, 11.2% were stored >30 minutes below 0°C and 33.2% were stored > 1 week above 8°C. Of all patients, 95% would accept redistributed medication when product quality is ensured.

Conclusion: During transport and home-storage, only one in eight biological injectors was stored within the recommended temperature range. This hinders redistribution of unused injectors, but also raises concern regarding drug effectiveness in IMID-patients.

INTRODUCTION

Over the past decades, the main direct healthcare costs in chronic immune-mediated inflammatory diseases (IMIDs) have shifted from outpatient visits, hospitalisation and surgery towards pharmacological treatment with biologicals¹⁻⁴.

Biologicals are complex human proteins that modulate the immune system by interfering with cytokine function, inhibition of T-cell activation, depletion of B-cells or by preventing migration of immune cells. The introduction of these drugs has significantly improved long-term outcome of IMIDs such as rheumatoid arthritis (RA), spondyloarthritis (SpA), inflammatory bowel disease (IBD) and plaque psoriasis.

Approximately 55,000 people in the Netherlands use biologicals for IMIDs, with prices ranging from €538 to €1159 per injector⁵, accounting for 623 million Euros per year⁶. Due to expanding indications for biologicals and advocating intensive treatment strategies aimed at complete remission of the disease, in which biologicals are frequently prescribed, further increase of costs is expected.

Strict guidelines exist for the production, storage and transportation of biologicals. According to the summary of product characteristics (SmPC), biologicals should be stored between 2°C and 8°C⁷⁻¹⁰. Extreme temperature conditions can lead to protein denaturation and may affect treatment effectiveness¹¹⁻¹⁴. Drug transport between manufacturer, wholesaler and pharmacy is monitored to guarantee product quality until dispensing. However, after the drug is dispensed to the patient, storage conditions are no longer monitored, precluding the guarantee of the product's safety and effectiveness.

When patients discontinue or switch biological treatment because of no response, loss of response or adverse events, 26-49% of the patients still have unused biologicals in their possession¹⁵. Currently, these injectors are destroyed and thus spilled accounting for millions of Euros lost each year¹⁶.

To reduce spillage, the number of injectors delivered to the patient at a time can be limited, however this results in more complex logistics and higher expenses both for pharmacies and patients. Alternatively, unused injectors could be redistributed. This requires proper storage, controlled distribution and guaranteed drug quality.

The aims of this study were to assess 1) the quality of transport and home storage by evaluating the proportion of biological injectors stored within the recommended temperature range and 2) acceptance of patients to receive redistributed injectors in order to prevent costly spillage.

METHODS

Design and study population

Between April and October 2015, all subcutaneous golimumab users, irrespective of the indication, at the Maastricht University Medical Centre+, were asked to participate in this prospective study. Patients used golimumab as prescribed by their physician, i.e. every 4 weeks, unless otherwise specified. During the study period, patients received three golimumab injectors at a time, stored in the original package. Each package for one single injector was wrapped in a sealed bag containing a validated temperature sensor. As usual, patients were instructed to store their medication in the fridge. After the study period, patients completed a questionnaire on their medication storage conditions at home and their opinion on potential redistribution of unused injectors.

Temperature sensor

The temperature sensor (AntTail, Utrecht, the Netherlands) was designed to specifically measure temperature in a home environment. The sensor measures the temperature every 5 minutes for a period up to 18 months. All sensors connect wirelessly to a router in the patient's home to transmit and store data to a secure cloud storage hosted by AntTail.

Temperature measurements

Deviations from the recommended range were defined as 1) > 30 minutes below 2°C or above 8°C or 2) any duration below 0°C. To distinguish transport from home storage, we defined "transport" as the period after distribution of the injector from the pharmacy until the first time the sensor measured a temperature below 8°C. If the temperature never exceeded 8°C after distribution from the pharmacy, it was assumed that the product was properly stored during transport. From the moment the temperature of the product was below 8°C, the product was considered "at home" (figure 1). We defined the moment of "use" when the temperature of the injector reached >15°C and did not return below 8°C.

Statistical considerations and data analysis

Demographic information was obtained from all patients at the time of recruitment and was presented using means (SD) and percentages of the study population. The quality of transport and home storage was assessed by the proportion of injectors stored within the SmPC recommended temperature range. Additional analyses were performed to assess the proportion of injectors stored below 0°C and above 20°C and to assess differences in storage conditions at home and during transport. Descriptive analyses were performed to evaluate the data from the patient questionnaires. Statistical analyses were done using SPSS statistics 22.0 (IBM, Armonk, NY, USA).

RESULTS

Storage conditions

In total, 50 patients received 276 injectors with temperature sensors that generated 2,466,576 measurements. Baseline characteristics of the patients are shown in table 1. The mean injector storage time was 30.9 ± 33.1 days. Figure 2 shows that only 11.6% ($n=32$) of the injectors were stored within the recommended temperature range (RTR). Temperature excursions occurred both during transport and at home (figure 3). During transport, one in five injectors was stored outside the RTR. At home, only one in six injectors was adequately stored. Sixty-seven (24.3%) injectors were stored below 2°C for >30 minutes. Of these, 31 (46.3%) were stored >30 minutes below 0°C (figure 4). A total of 223 injectors (80.8%) were stored above 8°C for >30 minutes. Of these, 81 (29.3%) were stored above 8°C for more than 1 week before use and 65 (23.6%) were ever above 20°C (figure 5). In all households at least one dispensed injector was stored outside the pre-defined range.

Table 1: baseline characteristics

	Participating patients (n=50)
Age, mean (SD)	53.2 (14.3)
Male gender, N (%)	21 (42.0)
Diagnosis, N (%)	
Crohn's disease	3 (6.0)
Ulcerative colitis	8 (16.0)
Rheumatoid arthritis	8 (16.0)
Spondyloarthritis	11 (22.0)
Psoriatic arthritis	20 (40.0)

Figure 1. Storage temperature curve.

Questionnaire

In total, 32 (64.0%) patients completed the questionnaire on home storage conditions and redistribution of unused biologicals. Of these patients, one patient (3.1%) stored the injector in the fridge-door, 8 patients (25.0%) in the vegetable drawer, 18 patients (56%) in the middle drawer and 5 patients (15.6%) on the top drawer of the fridge. Twenty-five patients (80.7%) found it comforting that storage conditions can be measured and 29 patients (96.7%) would appreciate an alarm when their biological is not adequately stored. Thirty patients (96.8%) are willing to accept unused medication when product quality is ensured. Twenty-eight patients (93%) believe that measuring storage conditions of biologicals could improve quality of healthcare.

Figure 2. Proportion of biologicals stored within the recommended temperature range (N, %).

Figure 3. Temperature excursions during transport and at home.

Figure 4. Temperature excursions below 2°C (N, %).

Figure 5. Temperature excursions above 8°C (N, %).

DISCUSSION

This study showed that, in patients' homes, only one in eight (11.6%) biological injectors was stored within the recommended temperature ranges, which hinders redistribution of unused biologicals. On the other side, when product quality is ensured, 96.8% of patients are willing to accept unused medication.

Previous observational studies on home storage conditions of temperature-sensitive drugs show similar alarming results. Cuellar et al. found that 58.3% of patients stored their biological injectors outside the recommended temperature range of 2–8°C for more than two hours¹⁷. Probably owing to a longer follow-up period and a stricter definition of storage conditions, Vlieland et al. found a higher percentage of 93.3% of patients not storing their injectors within the recommended temperature ranges¹⁸. In contrast to

the aforementioned studies, we packed each single injector with a temperature sensor in a sealed bag resulting in injector specific measurements. In addition, we distinguished between transport-storage and home-storage and added a questionnaire to the temperature measurements which provided insight on storage locations at patients' homes.

In our centre, patients receive their biological injectors at the hospitals' pharmacy in a cooler bag with a cold pack and are instructed to store their medication in the fridge. None of the patients achieved optimal storage, despite the fact that all patients who completed the questionnaire reported storage in the fridge during the study period. Improper storage may occur during transport or at home. Improper storage during transport might be due to storage too close to the cold pack, resulting in freezing of the product, or to too long of a delay before the injectors are placed in the fridge, resulting in melting of the cooling element and heating of the product. An explanation for improper storage at home may be that many household fridges have a 0°C vegetable drawer, which could lead to product freezing. In addition, Cuellar et al showed that an older fridge was a significant risk factor for inadequate storage, probably due to instability of the temperature¹⁷. Moreover, our study shows a large variation in storage conditions within one household suggesting temperature differences and fluctuations within the same fridge.

Storage outside the recommended temperature ranges and temperature fluctuations of these protein-based drugs may lead to protein denaturation and the irreversible formation of protein aggregates^{12, 19}. Protein aggregates may contribute to formation of anti-drug antibodies, which are found in 6-91% of patients on biological therapy^{14, 20-23} and are associated with adverse drug reactions¹¹ and a diminishing treatment effect over time in a significant proportion of patients^{24, 25, 26}.

For several other subcutaneous biologicals, i.e. adalimumab, etanercept and anakinra, it has been shown that injectors can be stored safely at temperatures up to a maximum of 25°C for a period of respectively 14 days⁸, 4 weeks¹⁰ and 12 hours⁹. Although this has not yet been studied for golimumab, it indicates that especially temperatures below 0°C, which occurred in our study in 12.3% of the injectors, may be harmful for product quality.

Limitations of this study were, firstly, that patients received 3 biological injectors per delivery during the study period. As a result, some injectors were only measured for a short period, possibly leading to an underestimation of our results. Secondly, assumptions were made regarding the transition from transport-storage to home-storage, the total home-storage time and the moment of injector use, which could have affected our results. Lastly, in this study we were not able to investigate the effect of improper storage on product quality, treatment effectiveness and disease outcomes. This has to be shown in future studies.

Although we only studied home storage of golimumab, the data of this study reflect patients' home storage behaviour and can therefore be generalized to other subcutaneous biologicals. Given the finding that in none of the households perfect storage within the recommended temperature range was achieved, it is unfortunately not possible to formulate a recommendation on the optimal storage place within the fridge.

In conclusion, the majority of golimumab users store their biological injectors outside the recommended temperature ranges. This precludes guaranteed drug quality, which not only hinders redistribution of costly, unused biologicals, but also raises concern regarding the effectiveness of the drugs in these patients. The exact consequences of storage outside the manufacturers' recommended temperature ranges on product quality and treatment effectiveness need to be investigated.

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Chapter 10

The prevalence of latent tuberculosis and hepatitis B after systematic screening of patients prescribed biological therapy in a low-endemic area

Marin de Jong, Danielle Roosen, Astrid van Tubergen

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LETTER TO THE EDITOR

We wish to provide some perspective with regard to the paper by Abitbol et al. entitled 'Negative screening does not rule out the risk of tuberculosis in patients with inflammatory bowel disease undergoing anti-TNF treatment: A descriptive study on the GETAID cohort'¹.

Biologicals are a powerful treatment for immune mediated inflammatory diseases (IMIDs), but associated with an increased risk for reactivation of latent infections such as tuberculosis (TB) or hepatitis B virus (HBV).² Several guidelines recommend screening before commencing biological therapy.³ Abitbol et al. demonstrated that a negative screening does not rule out the risk of TB infection in patients with inflammatory bowel disease (IBD) undergoing anti-TNF therapy.¹ In a retrospective study among 20 Swiss and French centres between 2001-2015, in total 44 IBD patients undergoing anti-TNF treatment, in whom the initial screening was negative, were identified with TB.

From our research we would like to emphasise not only the importance of screening, but also the monitoring during therapy. At our centre, located in a low-endemic area, we have implemented a hospital-wide systematic screening for all patients commencing biological therapy since 2012. The screening consists of a detailed medical history on risk factors for TB (i.e. previous diagnosis of TB, contact to a TB-infected person, previous living and travelling outside developed countries) and HBV (i.e. occupation, intravenous drug abuse, sexual behavior), interferon-gamma release assay (IGRA), HBV serology (i.e. HBs-Ag, anti HB-core) and a chest X-ray. To monitor patients during biological therapy, we developed MyBiologicalCoach, a telemonitoring system that, among other patient-reported outcome measures, systematically screens for risk of infections and side-effects every 3 months.

From May 2012 through July 2015, 547 of 549 patients (99.6%) prescribed biological therapy were screened, of whom 22 (4.0%) tested positive on IGRA and were classified as having latent TB. Of these, 14 did not report any risk factor, 18 had always lived in the Netherlands and another 18 never travelled outside developed countries. Four patients had abnormalities on chest X-ray, 3 of them also tested positive on IGRA and the other one was diagnosed with sarcoidosis. All latent TB patients were treated with isoniazid and biological therapy was started. After a mean follow-up period of 30.9 ± 8.8 months none of the patients showed a reactivation of TB. One patient (0.2%) tested positive for HBV without any risk factor; he did not commence biological therapy.

In contrast to the study by Abitbol et al., in which screening for latent TB was in most cases (57%) performed using TST only, we used IGRA in all cases, which shows fewer false negative results.⁴ Despite this, the results underscore the importance of screening and monitoring for latent TB and HBV in IMID patients, even in a low endemic area.

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Chapter 11

General discussion

Inflammatory bowel disease (IBD) is a chronic condition of the gastrointestinal tract with Crohn's disease (CD) and ulcerative colitis (UC) as the main phenotypes. IBD patients risk recurrent unpredictable flares, complications, frequent surgeries and hospitalisations, and therefore the impact on patients' quality of life is high. Due to the early onset and chronicity, IBD profoundly affects educational level and work productivity with accompanying economic losses accounting for up to 31% of the total IBD-related healthcare costs¹. The direct healthcare costs for IBD in the Netherlands exceed 300 million euros yearly. Despite significant advances in the management of IBD over the past decades, there is still no curative treatment and standard disease management based on treating symptoms alone did not sufficiently improve long-term outcome. Jeuring et al. assessed the impact of changing medical treatment options and management strategies over the past three decades on long-term disease outcomes in the Dutch IBD South Limburg cohort. This population-based study found that more recently diagnosed CD patients, i.e. diagnosed after the introduction of biologicals, had lower hospitalisation and surgery rates and fewer days of corticosteroid exposure during their disease course. This occurred in parallel with earlier and more frequent exposure to immunosuppressives and biologicals. However, despite high exposure to these costly drugs, the risk of disease progression from an inflammatory to a stricturing or penetrating phenotype has not changed over time². Furthermore, data on work productivity and quality of life are lacking in these epidemiological studies. To further improve outcomes and prevent disease progression, more intensive management strategies focusing on tight control and tight monitoring have been studied and validated⁽³⁾. Other proposed strategies address interventions on aspects that might influence disease activity, such as non-adherence to treatment, unfavourable nutritional status, smoking, and psychological factors. Implementation of such a holistic management strategy in the current traditional healthcare organisation is however challenging. Therefore, reorganisation of IBD healthcare is warranted. At the start of this project we hypothesised that tight remote monitoring of disease activity and other patient-reported outcome measures (PROMs) through telemedicine could improve the outcome and quality of care for IBD. In this thesis, we showed the results of several studies to validate this hypothesis.

Remote monitoring of inflammatory bowel disease activity

Mounting evidence shows that tight control of (sub)clinical mucosal inflammation is the key towards blocking disease progression and irreversible bowel damage resulting in complications, such as strictures, abscesses and fistulae⁴. These complications and subsequent surgery are the major drivers of impaired quality of life in IBD. Successful remote monitoring of disease activity requires PROMs validated to endoscopy, which is the gold standard to assess mucosal inflammation. The USA Food and Drug Administration has provided guidelines for development and validation of PROMs. They recommend that

at least content validity (the extent to which an instrument measures the concept of interest), construct validity (relationships with another accepted measures of disease activity), criterion validity (the extent to which a PROM is related to a generally accepted gold standard measure), reliability (the extent to which the PROM yields consistent scores over time when no change is expected in disease activity) and responsiveness to change (the ability of a PROM to detect differences in scores over time) have to be investigated⁵. An extensive literature search for available PROMs measuring IBD activity was performed and presented in **chapter 2**. A systematic review of these PROMs showed that none of them met all the FDA recommendations for PROM-development. Only two articles reported on content validity and none of the reviewed PROMs was developed compared to endoscopy.

Therefore, we developed and validated a new PROM following the FDA recommendations and relative to endoscopy (**chapter 3**). The main purpose of this PROM was to identify patients at risk for active disease. Therefore, a sensitivity of at least 85%, while maintaining sufficient specificity, was endeavored. The measurement properties of the newly developed PROM, the Monitor IBD At Home (MIAH) questionnaire, compared to endoscopy were unsatisfactory (sensitivity and specificity of 67.6% and 81.3% for CD patients and of 68.2% and 80.5% for UC patients, respectively) and comparable with the previously developed patient-reported mobile health index(6). This underscores the findings in the literature that symptoms only moderately correlate with endoscopic findings; 30% of IBD patients in clinical remission show endoscopic inflammation, and a substantial portion of IBD patients have IBS-like symptoms and positive clinical activity scores, without having mucosal inflammation^{7,8}. A combination of clinical symptoms and biochemical biomarkers, such as C-reactive protein, thrombocytes, and especially fecal calprotectin, is able to improve the performance^{9,10}, however the need for patients to visit the hospital or send fecal samples per mail still exists. Recently, a fecal calprotectin home-test was introduced and in **chapter 3**, we describe the performance of a combination of the MIAH questionnaire and the fecal calprotectin home-test. This combination improved the diagnostic accuracy to a sensitivity, specificity, positive predictive value and negative predictive value of 96.7%, 66.7%, 76.3% and 94.7% for CD patients and of 88.2%, 71.4%, 60.0% and 95.6% for UC patients, respectively, and thereby allows for close monitoring mucosal inflammation at home.

Development of a new telemedicine system for all IBD patients

Over the past decade, several trials assessed the possibilities of telemedicine to improve the outcome of IBD (see table 3, chapter 4)¹¹⁻²⁰. However, the telemedicine systems available at the start of our project were only suitable for specific subtypes of IBD, focused mainly on mild-to-moderate disease, and showed inconsistent results in trials. Furthermore, most systems lacked a framework for development (patient and clinician

input), evaluation (methodology and trial outcomes), and implementation (financial and logistic hurdles, patients' and/or clinicians' resistance to change) compromising their implementation in routine clinical practice²¹. In **chapter 4**, we describe the systematic development of the first telemedicine system, myIBDcoach, which enables home-monitoring of all subtypes of IBD patients. Through an iterative process with patients, nurses and gastroenterologists, monitoring modules were designed, and topics for e-learning modules selected. MyIBDcoach is ISO-certified, compliant with all European laws and therefore safety and privacy are guaranteed. A pilot study with myIBDcoach proved that the tool was feasible for use in routine care and well-accepted by patients and healthcare providers. Patients were compliant with the program, indicated that myIBDcoach facilitated communication with their healthcare providers and that the e-learning modules improved their knowledge about IBD (**chapter 4**).

Reorganisation of IBD-care with telemedicine

IBD care is traditionally organised by standard scheduled outpatient visits, with a frequency predominantly based on medical treatment and local policy, but independent of the occurrence of unpredictable flares. This might result in an inefficient and potentially costly way of medical resource use and patients' time. In addition, as abovementioned, treatment strategies for IBD are shifting from mere management of symptoms towards tight and personalised control of intestinal inflammation and timely intervention when inflammation (re-)occurs. This, together with the rising incidence of IBD, results in overburdened IBD clinics and escalating costs. The direct healthcare costs for IBD are mainly driven by medication costs, hospitalisations and outpatient clinic visits^{1, 22, 23}. Structural healthcare reorganisation is warranted to improve efficiency of care, enable implementation of new management strategies in an overburdened healthcare setting, and constrain healthcare costs. Our hypothesis that telemedicine, when combined with adjustments in outpatient processes, contributes to quality of care improvement for IBD patients was studied in chapters 5 and 6.

In **chapter 5** we show that telemedicine enables healthcare professionals to implement a tight control strategy in IBD patients, while reducing the number of outpatient visits. This reduction in required outpatient visits frees up capacity at outpatient clinics to guarantee adequate access for those patients with complex disease or in need of urgent intervention. Additionally, telemedicine transforms traditionally scheduled outpatient care to on demand healthcare which enhances patient-empowerment. Tight monitoring, furthermore, allows for early detection of disease activity, early intervention in case of a relapse, and minimisation of the delay to treatment initiation. In our study we found that close monitoring with telemedicine reduced the number of hospital admissions, despite the same number of flares in both the intervention and control group, prudently suggesting that early detection of flares and early treatment interventions

in combination with efficient communication might prevent hospital admissions. Trials with longer follow-up periods are required to determine whether telemonitoring can alter disease progression and improve long-term disease outcomes. The pragmatic study design of the myIBDcoach trial closely resembles routine practice in the Netherlands and facilitates implementation of novel telemonitoring care pathways in routine care as described in the valorization chapter in this thesis.

As described in chapter 5, telemedicine reduces outpatient visits by 36% and hospitalisations by 50%. This suggests that implementation of telemedicine could reduce healthcare costs. The results of a trial based cost-effectiveness analysis presented in **chapter 6** indeed showed that telemedicine with myIBDcoach resulted in lower mean yearly costs of €547 per patient (95%CI, [€-1,029, €2,143]; mean costs of €9481 for standard care and €8934 for telemedicine).

Besides telemonitoring, myIBDcoach provides patient-tailored information (i.e. on medication adherence, nutrition, or smoking), a personal care plan, registration of PROMs, and easily accessible contact with the IBD nurse. After 12 months use of myIBDcoach, we found that medication adherence significantly improved. Non-adherence is a well-known phenomenon in IBD patients and is reported to be as high as 40%-60%²⁴. It has a significant impact on the risk of disease relapse, hospitalisation, colorectal cancer and thereby on healthcare costs and work absenteeism^{20, 25-27}. In addition, for 5-ASA use, annual healthcare costs were found to be 12.5% higher in non-adherent patients compared to adherent patients, despite increased medication expenditures(28). Also for non-adherent infliximab users, annual costs were 12% higher mainly due to more frequent outpatient visits, hospitalisations and emergency room visits(26). Several efficacious interventions have been reported to improve adherence to medication. First, disease-specific education on management algorithms and medical therapies have previously been shown to increase adherence^{18, 25}. Second, guided self-management with personalised action plans in case of a relapse showed to improve UC patient-empowerment and medication adherence^{18, 29}. Implementation of such action plans in myIBDcoach, by which patients could immediately self-initiate treatment in case of symptoms, could further reduce the treatment delay and duration of flares and thereby the risk of disease progression. Furthermore, factors such as malnutrition, smoking, psychological problems, stressful life events and poor social support are considered to affect disease activity and quality of life(30). Collection of PROMs on these factors create awareness among both healthcare providers and patients. Development of standard procedures and education programs for all these aspects could further improve the long-term outcome of IBD in the future.

In **chapters 7-9** we show that, by systematic measurement of patient-reported outcomes, valuable information on disease-related aspects as nutrition, psychological

wellbeing, medication adherence, and medication side-effects, can be generated and used as leads for interventions on these aspects.

Implementation and value for clinical practice

Although the myIBDcoach trial convincingly showed that telemedicine reduces health-care utilisation and costs while maintaining quality of care, broad implementation is currently hindered by a few barriers⁽³¹⁾. The main obstacle is reimbursement; implementation of telemedicine is accompanied by initial costs, by structural license fees and by inevitable changes in the organisation of IBD units where tasks will need to be shifted from gastroenterologists to specialised nurses. If costs are not reimbursed, broad use of innovative care with telemonitoring will be unlikely. Therefore research focusing on economic evaluation of telemedicine interventions is important to help decision makers estimate the value of healthcare reorganisation with telemedicine towards reimbursement.

Currently, healthcare providers in the Netherlands receive one fixed payment that includes all services a patient may need during a period of time, but requires physical outpatient visits (volume-based payment). For eHealth consultations, however, efforts are not yet rewarded accordingly. In this context, value-based instead of volume-based care, is gaining ground. The key concept behind value-based healthcare is to improve quality of care while controlling costs, and reward high-value care instead of volume^{32, 33}. Improving quality of care is a continuous task for healthcare professionals and institutions. However, perspectives on what good quality of care is might differ between patients, healthcare workers, governments and hospitals (table 1). In literature, quality of care is commonly defined as a multifaceted goal aimed at improving disease outcomes by consistent delivery of evidence-based care to all patients, and decreasing practice variability leading to better individual outcomes, a healthier population and reduced costs (the triple aim)⁽³⁴⁻³⁶⁾. Over the recent years, additionally, the subjective perception of health by patients is playing an increasingly important role in the assessment of quality and value of care^{37, 38}.

Quality can be measured using quality indicators (structure indicators, process indicators or outcome measures). Structure indicators are related to the structure of care delivery and describe the availability of healthcare professionals such as gastroenterologists, IBD-nurses, healthcare facilities and remote monitoring and communication tools. Process measures are related to the process of care delivery, for example the percentage of patients screened for tuberculosis prior to anti-TNF treatment (**chapter 10**). Outcome measures are related to the outcome of the delivered care, including PROMs that are related to outcomes that matters most to patients^{32, 33}.

In order to improve quality of care, and to benchmark and evaluate practice variation, systematic measurement of quality indicators as well as PROMs and patient-experiences

is thus increasingly advised. For IBD, quality indicators are defined by the European Crohn's and Colitis Organisation, the IBD section of the NVMDL (Dutch organisation of gastroenterologists), and the International Consortium for Health Outcomes Measurement (ICHOM)^{32, 37}. In this regard, healthcare workers are increasingly requested to register patients' perspectives with PROMs and quality indicators, which is challenging in an overburdened healthcare setting. A telemedicine system such as myIBDcoach enables automatic registration of quality indicators (the standard ICHOM set for IBD is available in myIBDcoach) and PROMs and thereby assists hospitals to implement value-based healthcare programmes.

Table 1. Perspectives on what good quality of care is might differ between patients, healthcare workers, governments and hospitals.

Patients	Long-term disease outcome		Healthcare workers
	Quality of life Personalised care Patient-tailored information Good communication Patient-empowerment Disability Work productivity	Implementation of a tight control strategy Monitoring of disease-affecting factors for targeted interventions Registration of quality indicators Research	
Governments	Accessibility of healthcare Indirect healthcare costs Registration of quality parameters	Safety of care Research	Hospitals
	Direct healthcare costs		

Directions for future IBD care

Over the past decades treatment of IBD changed due to registration of an increasing number of new (biological) drugs, more aggressive management strategies, and targeted therapies. The current patient-stratification of this heterogeneous disease, based on clinical characteristics, however, does not adequately predict the disease course and lacks genetic and molecular markers. Overtreatment of patients with a favourable outcome is expensive and puts them at risk of possible severe side-effects of immunosuppressive treatments. Undertreatment of patients with an aggressive phenotype and delay of introduction of highly effective biologicals might lead to disease progression, surgery, hospitalisations and impaired quality of life.

Continuous collection of data from large cohorts on patients' characteristics, classic outcomes, PROMs and biomarkers via hospital information systems and telemedicine tools and converting these data into information can aid towards better patient stratification and personalised care pathways. Subsequent implementation of personalised management strategies, by which the most accurate treatment can be chosen for the

right patient, at the right location at the right time, might reduce the under- or overuse of resources and control costs.

Remote monitoring of PROMs, furthermore, allows registration of disease-related factors that might influence disease activity such as stress, smoking and malnutrition (**chapters 7 and 8**). Telemedicine tools with inbuilt alarm triggers, such as myIBDcoach, create awareness on these factors and enable targeted intervention. In our clinic, currently 2 pilot studies are carried out with personalised intervention strategies. First, the e-learning module “stop smoking” is offered through myIBDcoach to all patients who actively smoke. After completion of this module, patients are contacted by an IBD-nurse and asked if they are motivated to stop smoking. If willing, patients are directly referred to the specialised “stop smoking” outpatient clinic. Secondly, fatigue is systematically monitored by myIBDcoach. In case of disabling complaints of fatigue, when a patient is in clinical and biochemical remission and when anemia is excluded, an intervention by a sport physiotherapist to improve physical condition is offered. In the near future, systematic interventions on work related problems and anxiety disorders will be evaluated. At present myIBDcoach is used in 17 hospitals in the Netherlands. The improved care-pathways based on data-analytics are shared and continuously improved within this network in close collaboration with the Dutch patient organisation (Crohn en Colitis Vereniging Nederland (CCUVN)).

Due to changes in treatment strategies towards often and earlier prescription of immunosuppressives, the number of patients exposed to immunosuppressives has exponentially increased. This leads to higher direct healthcare costs, but also raises concern about safety and side-effects. Currently, trials are investigating whether de-escalation of therapy is safe, whether subgroups of patients can be identified for whom de-escalation is most beneficial, and whether risk factors for recurrence of disease after de-escalation can be identified(3). In patients who discontinue treatment, close monitoring of disease activity is warranted to enable timely intervention in case of a relapse. In this situation, myIBDcoach together with home fecal calprotectin measurement offers unique opportunities for monitoring of IBD after treatment de-escalation.

Concluding remarks

Improving long-term outcome, quality of care and controlling costs is the responsibility of every healthcare facility treating patients with IBD. This thesis offers new insights into the use of remote monitoring to enable more efficient and affordable healthcare for chronic conditions. Implementation of telemedicine in IBD care bridges the gap between the healthcare professionals’ requests for tight disease-monitoring and continuity of care in an overburdened outpatient setting and patients’ demands for more involvement in disease management. Combining the current and future findings, tele-

medicine systems can be a valuable tool for reorganising IBD care towards personalised and value-based healthcare (figure 1).

Figure 1. Schematic overview of the different functions of myIBDcoach, and on how these different functions together might result in an effective tool towards value-based healthcare. The straight lines were proven effective in this thesis; the dotted lines have to be investigated in future long-term studies.

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Epilogue

SUMMARY

Inflammatory bowel diseases (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory disorders of the gastrointestinal tract characterised by periods of exacerbation and remission. The current treatment target for IBD is to achieve and maintain steroid-free clinical remission and to prevent structural bowel damage, such as fistulas, abscesses, intestinal strictures, and surgery. To achieve these targets, recent guidelines advocate more stringent management, involving tight control of disease activity and early intervention in patients with intestinal inflammation. Other interventions address aspects of inflammatory bowel disease that may influence disease activity, such as non-adherence to treatment, unfavourable nutritional status, smoking, and psychological factors. These personalised interventions were shown to reduce the rates of disease relapse, healthcare utilisation and absence from work in subsets of patients, but have not been systematically implemented in routine care. Implementing such a tight and personalised control strategy puts substantial pressure on patients' time and the capacity of outpatient clinics and it remains challenging to acquire all necessary information at the right moment for each individual patient. Furthermore, the heterogeneous nature of inflammatory bowel disease, combined with an absence of adequate markers for patient stratification, leads to under- or overuse of resources and subsequent costs. In this regard, telemedicine systems are promising to aid healthcare workers in implementing a tight control strategy and optimise efficiency of care at the same time. Telemedicine systems which have been used to manage chronic diseases, such as congestive heart failure and chronic obstructive pulmonary disease, allow for the strict and instantaneous follow-up of health parameters and timely, personalised interventions. Moreover, these systems can provide tailored information based on each patient's needs. This thesis focuses on telemedicine for IBD and describes the development of myIBDcoach, the first telemedicine system that monitors and registers disease activity in patients with all subtypes of inflammatory bowel disease.

Part I: development of a telemedicine system for inflammatory bowel disease

To facilitate broad implementation, myIBDcoach was developed for all subtypes of IBD patients, using a structured iterative process among the developer, delegates from the Dutch inflammatory bowel disease patient organisation (CCUVN), nurses, and gastroenterologists working in secondary and tertiary referral centres.

The first step in this process was to select valid patient-reported outcome measures (PROMs) to monitor disease activity and other disease-modifying factors, such as medication adherence, psychosocial factors and nutrition. In the context of tight control, PROMs monitoring IBD disease activity should accurately reflect mucosal inflammation and should be suitable for frequent and remote monitoring. An extensive literature

review (chapter 2) on PROMs for IBD disease activity showed that none of the available PROMs met the criteria for PROM-development from the Food and Drug administration (FDA): at least data regarding *content* validity (patients' input and experience), *construct* validity (relationship with other accepted measures of disease activity), *criterion* validity (relationship with golden standard, i.e. endoscopy), *reliability* (measurement properties over time) and the *ability to detect changes over time* should be evaluated to determine their utility for clinical practice. In this regard, we decided to develop a new patient-reported disease activity score following the FDA criteria. We found that a 5-item patient-reported questionnaire for UC and a 6-item patient-reported questionnaire for CD in combination with a fecal calprotectin home-test could predict mucosal inflammation with a fecal sensitivity and specificity of 96.7% and 66.7% for CD patients and 88.2% and 71.4% for UC patients (chapter 3).

Besides continuous home-monitoring of disease activity and disease-related aspects (medication adherence, side-effects, malnutrition, smoking, quality of life, fatigue, life-events, work participation, stress, and anxiety and depression), myIBDcoach optimises disease knowledge and communication between patients and healthcare providers. The system furthermore provides e-learning for patient empowerment. A pilot study with myIBDcoach proved that the tool was feasible for use in routine care and well-accepted by patients and healthcare providers. Patients graded the system with a mean of 7.8 of 10, and 93% would recommend myIBDcoach to other patients (chapter 4).

Part II: efficacy of telemedicine for inflammatory bowel disease

To evaluate the efficacy of telemedicine, we performed a pragmatic randomised multicentre trial in which telemedicine with myIBDcoach was compared to standard outpatient care. This trial, in which an unselected heterogeneous group of 909 IBD patients was included, showed that personalised telemonitoring reduced the number of outpatient visits by 36%, and the number of hospitalisations by 50%, while increasing adherence to medication (chapter 5). A cost-utility analysis showed that telemedicine with myIBDcoach was cost-effective and resulted in lower mean annual costs of €547 per patient, with equal quality of life. These data underscore the value of telemedicine for healthcare reorganisation towards more efficiency (chapter 6).

Part III: personalised care with telemedicine

Besides healthcare reorganisation, telemedicine enables continuous collection of data on quality metrics and patient-reported outcomes. This thesis shows that by systematic measurement of these outcomes, valuable information on disease-related aspects as nutrition, psychological wellbeing, medication adherence, and medication side-effects becomes available and can be used for timely personalised interventions. As described in chapters 7 and 8, novel perceived stress and an impaired nutritional status were

identified as risk factors for future flares. During current traditional outpatient visits, these topics are often not discussed due to time constraints. Telemedicine can also be used to improve medication adherence and to monitor and improve medication storage behaviour (chapter 9). For IBD patients who use biologicals, we additionally developed a biological monitor which systematically screens for risk factors on latent tuberculosis and hepatitis B and monitors medication side-effects. These data could be used for evaluation of care processes and optimisation of country-specific screening and vaccination protocols for patients using biologicals.

In conclusion, telemedicine systems are valuable to reorganise IBD care towards personalised and value-based healthcare. This thesis offers new insights into the use of remote monitoring to enable more efficient and affordable healthcare for IBD. Implementation of telemedicine bridges the gap between the healthcare professionals' requests for tight and personalised disease-monitoring and continuity of care in an overburdened outpatient setting and answers to patients' demands for more participation in disease management.

SAMENVATTING

Dit proefschrift had tot doel meer inzicht te verkrijgen in de mogelijkheden van telemedicine voor management van inflammatoire darmziekten ("inflammatory bowel diseases", IBD). De ziekte van Crohn (CD) en colitis ulcerosa (UC) zijn chronische inflammatoire aandoeningen van het maagdarmkanaal en worden gekenmerkt door perioden van exacerbatie en remissie. Beide aandoeningen kunnen zich heterogeen presenteren, zoals blijkt uit verschillen in ziektelocatie, respons op behandeling en het optreden van complicaties. Het klassieke behandeldoel voor IBD is gericht op het verkrijgen van steroïde-vrije klinische remissie en om dit te behouden ter voorkoming van structurele darmbeschadiging, zoals fistels, abcessen, intestinale stricturen en operaties. Traditioneel bestaat de IBD zorg uit geplande routine polikliniek bezoeken met een frequentie die vooral is gebaseerd op de medicamenteuze behandeling en extra afspraken wanneer er een toename van klachten is. Echter, behandeling op basis van symptomen alleen heeft de ziekte-uitkomsten op lange termijn (aantal opvlammingen, corticosteroïd gebruik, ziekenhuisopnames en operaties) de afgelopen 20 jaar onvoldoende verbeterd. Daarom adviseren recente richtlijnen strengere monitoring van mucosale inflammatie en vroegtijdige interventie bij een opvlamming; de zogenaamde *tight control* strategie. Hiervoor is frequente controle van ziekteactiviteit noodzakelijk. Daarnaast worden vele relevante ziekte-aspecten, zoals therapietrouw, voedingstoestand en psychische klachten door de meeste MDL-artsen niet systematisch gevolgd terwijl monitoring en behandeling hiervan kan resulteren in betere ziekte-uitkomsten. Verzekeringsmaatschappijen, overheden en patiëntenorganisaties vragen steeds vaker om registratie van patiënt-gerapporteerde uitkomstmaten ("patient-reported outcome measures", PROMs), patiënt-gerapporteerde ervaringen en kwaliteitsparameters ter evaluatie van dure behandelingen. In de huidige organisatie van IBD zorg is registratie van al deze informatie op het juiste moment voor iedere individuele patiënt meestal niet haalbaar. Reorganisatie van de IBD zorg is daarom noodzakelijk, zeker omdat de incidentie van IBD stijgt.

Telemedicine maakt het door middel van monitoring op afstand mogelijk een *tight control* strategie te implementeren, waarbij gezondheidsparameters frequent kunnen worden gemonitord en onmiddellijke follow-up in de vorm van gepersonaliseerde interventies mogelijk is. Voor chronische obstructieve longziekten en hartfalen werden eerder al gunstige resultaten van telemedicine op de ziekte-uitkomsten gezien. Dit proefschrift richt zich op telemedicine voor IBD en beschrijft de ontwikkeling van mijnIBDcoach, de eerste telemedicine tool voor alle IBD patiënten.

Deel I: ontwikkeling van een telemedicine tool voor inflammatoire darmziekten

De eerste stap in de ontwikkeling van een telemedicine tool was het selecteren van gevalideerde PROMs ten aanzien van ziekteactiviteit, maar ook ten aanzien van ziekteaspecten zoals therapietrouw, voedingstoestand en psychosociale factoren. PROMs gericht op het monitoren van ziekteactiviteit zijn idealiter gevalideerd ten opzichte van endoscopie (de gouden standaard voor het beoordelen van mucosale inflammatie) en geschikt voor frequent gebruik op afstand. Een uitgebreid literatuuronderzoek (hoofdstuk 2) toonde dat de beschikbare PROMs om IBD ziekteactiviteit te monitoren niet voldeden aan de criteria voor PROM-ontwikkeling van de Food and Drug Administration (FDA): om de klinische toepasbaarheid te evalueren moeten ten minste gegevens bekend zijn ten aanzien van de *content* validiteit (input en ervaring van patiënten), *construct* validiteit (relatie met andere geaccepteerde meetinstrumenten voor ziekteactiviteit), *criterium* validiteit (relatie met de gouden standaard (in dit geval endoscopie)), betrouwbaarheid (consistentie in het produceren van gelijksoortige resultaten onder gelijke condities) en het vermogen om veranderingen in ziekteactiviteit over een tijdsperiode te meten. Hoofdstuk 3 beschrijft de ontwikkeling van een nieuwe PROM voor het meten van ziekteactiviteit volgens de FDA-criteria. De monitor IBD at home score, een 5-item vragenlijst voor UC en een 6-item vragenlijst voor CD in combinatie met een fecaal calprotectine thuistest kan mucosale inflammatie voorspellen met een sensitiviteit en specificiteit van 96.7% en 66.7% voor CD-patiënten en 88.2% en 71.4% voor UC-patiënten.

De volgende stap bestond uit het vormgeven van de overige functies van de nieuwe telemedicine tool mijnIBDcoach. MijnIBDcoach is een persoonlijke webpagina en monitort naast ziekteactiviteit ook PROMs ten aanzien van therapietrouw, voedingstoestand, rookgedrag, bijwerkingen van geneesmiddelen, arbeidsparticipatie, kwaliteit van leven en angst en depressie. Gebruikers worden periodiek uitgenodigd een vragensessie in te vullen waarvan de resultaten worden samengevat in een behandeloverzicht. Wanneer antwoorden een alarmgrens overschrijden, zorgen ze voor een signaal in de backoffice in het ziekenhuis waar de patiënt onder controle is. Er kan dan direct een behandeladvies worden gegeven, aanvullend onderzoek worden ingezet of worden besloten een afspraak op de polikliniek te maken. Gebruikers kunnen ook berichten sturen via de beveiligde netwerkomgeving. Naast de monitoringsfunctie biedt mijnIBDcoach een brede waaier aan kennismodules aan, zoals over zelfmanagement, geneesmiddelen, stoppen met roken, voeding en het belang van therapietrouw. Een pilotstudie liet zien dat zowel patiënten als zorgverleners erg tevreden waren over het gebruik van mijnIBDcoach en dat de compliantie met het systeem hoog was (hoofdstuk 4).

Deel II: effectiviteit van telemedicine voor inflammatoire darmziekten

Het effect van mijnIBDcoach werd na de pilotstudie onderzocht en in een gerandomiseerde multicenter studie waarin telemedicine werd vergeleken met de reguliere zorg. Deze studie, waarin een niet-geselecteerde heterogene groep van 909 IBD-patiënten was opgenomen, toonde aan dat patiënten door gepersonaliseerde telemonitoring significant minder (36%) vaak op de polikliniek bij de MDL-arts en verpleegkundige hoefden te komen en het aantal ziekenhuisopnames met 50% verminderde (hoofdstuk 5). Verder was het gebruik van mijnIBDcoach veilig: de studie toonde geen verschillen aan tussen beide groepen met betrekking tot het aantal opvlammingen van de ziekte, het gebruik van corticosteroïden als rescue medicatie, het aantal SEH bezoeken en het aantal IBD gerelateerde operaties. Patiënten in de mijnIBDcoach groep waren even tevreden over de kwaliteit van de zorg als de patiënten in de reguliere zorg groep. Ten slotte zagen we dat de therapietrouw significant verbeterde onder patiënten die mijnIBDcoach gebruikten.

De belangrijkste redenen genoemd in de literatuur waarom eHealth toepassingen nog niet op grote schaal zijn geïmplementeerd, zijn onvoldoende samenwerking tussen IT-ontwikkelaars en gebruikers (hulpverleners/patiënten) bij de ontwikkeling, de ontwikkeling van systemen voor kleine niches/specifieke (kleine) patiënten categorieën en vooral het gebrek aan goede studies die de effecten, maar ook kosten van eHealth systemen aantonen. Om deze reden werd mijnIBDcoach ontwikkeld in nauwe samenwerking met artsen, IBD-verpleegkundigen en de patiënten van de Crohn en Colitis Ulcerosa Vereniging Nederland en is het programma geschikt voor monitoring van alle typen IBD patiënten. Een kosten-utiliteitsanalyse toonde aan dat telemedicine met myIBDcoach kosteneffectief was en resulteerde in een gemiddelde kosten reductie van €547 per patiënt per jaar met gelijkblijvende kwaliteit van leven en verbetering van kwaliteit van zorg. Deze gegevens ondersteunen de waarde van telemedicine voor reorganisatie van de gezondheidszorg (hoofdstuk 6).

Deel III: gepersonaliseerde zorg met telemedicine

Naast reorganisatie naar doelmatigere zorg maakt telemedicine continue registratie van gegevens mogelijk voor kwaliteitsmetingen en onderzoek. Dit proefschrift laat zien dat door systematische registratie van PROMs waardevolle informatie kan worden gegenereerd en kan worden gebruikt als aanknopingspunt voor gepersonaliseerde interventies. Zoals beschreven in hoofdstukken 7 en 8 blijken stress en een verminderde voedingsstatus een risicofactor voor het uitlokken van opvlammingen. Tot dit moment bleven deze onderwerpen vaak onderbelicht in een regulier polikliniekbezoek. Patiënten die mijnIBDcoach gebruiken ontvangen voorafgaand aan een polikliniekbezoek een vragenlijst die klachten op fysiek, emotioneel, sociaal of praktisch vlak onder de aandacht brengt. Dit maakt een poliklinisch bezoek aan de MDL-arts efficiënter en pa-

tiëntgerichter en garandeert daarmee dat alle relevante onderwerpen worden besproken en dat patiënten waar nodig naar andere specialisten kunnen worden doorverwezen. Telemedicine kan ook worden gebruikt om het gedrag rondom medicatie-inname te evalueren en door middel van interventies daarop kan therapietrouw verder worden verbeterd (hoofdstuk 9). Voor IBD-patiënten die biologicals gebruiken werd mijnBiologicalcoach ontwikkeld: een extra module die systematisch risicofactoren voor latente tuberculose en hepatitis B screent voorafgaand aan start van biological therapie en daarnaast de bijwerkingen van deze medicatie monitort (hoofdstuk 10). Deze gegevens kunnen worden gebruikt voor de evaluatie van zorgprocessen en de optimalisatie van landelijke screening- en vaccinatieprotocollen voor patiënten die biologicals gebruiken.

Dit proefschrift biedt nieuwe inzichten in het gebruik van telemedicine teneinde de IBD zorg te reorganiseren naar gepersonaliseerde en doelmatigere zorg. Implementatie van telemedicine slaat een brug tussen de wens van hulpverleners om een tight control strategie te implementeren voor de groeiende groep IBD-patiënten ondanks beperkte middelen en de vraag van patiënten naar meer participatie bij hun behandeling. Daarnaast biedt het programma mogelijkheden om de zorg te verbeteren door registratie van PROMs en kwaliteitsparameters die gebruikt kunnen worden voor value-based healthcare.

VALORISATION

Inflammatory bowel disease (IBD) is a chronic heterogeneous condition of the gastrointestinal tract that requires life-long continuous and tight monitoring to prevent complications such as fistulae, abscesses, surgeries and hospitalisations. The disease itself and especially these complications are responsible for a diminished quality of life in IBD patients. In the current traditional overburdened outpatient setting, implementation of a tight control strategy is challenging and costly. Optimisation of quality of care is an important task of healthcare professionals and facilities but due to increasing healthcare expenditures, professionals are stimulated to develop innovative and creative ideas to improve outcome and quality of care but control costs. This thesis showed that telemedicine enables implementation of a tight control strategy resulting in better health outcomes without increasing healthcare costs.

Value for patients

Value of care for patients is determined by two factors: health outcomes and healthcare costs¹. This thesis showed that both factors were positively influenced by the use of telemedicine. The myIBDcoach trial showed that care via telemedicine contributed to strict monitoring and instantaneous action in case of a relapse. Most probably this was responsible for the 50% reduction in hospitalisations and thereby better health outcome. As expected, incorporation of telemedicine in IBD-care resulted in cost-savings. Furthermore, patients reported that myIBDcoach resulted in time-savings because they only had to visit the hospital when necessary and they could fill out monitoring sessions at a for them convenient moment and location. A recently performed survey among 7500 IBD patients highlighted 5 areas related to quality of IBD care from the patients' perspective: (1) quality of specialist communication, (2) whether the review consultation was long enough, (3) failure to share information in the past 2 years, (4) no access to a dietitian and (5) speed of advice in case of flare². As patients were involved in this project from the early beginning, myIBDcoach also monitors outcomes that matter most to them, such as quality of life, nutrition, (work)disability and psychological problems. Monitoring on these aspects enables professionals to implement a more personalised and holistic treatment approach with targeted interventions, such as a referral to physiotherapists, dietitian or a psychologist. We furthermore expect that due to the information function of myIBDcoach and due to insight in their personal care plan, patients' self-management and empowerment will be improved. From the literature, we know that this positively influences quality of

Patient: MyIBDcoach helps to keep track of my illness and I can find information easily. If it goes bad, the line with your doctor is very short and prevents you from waiting too long with serious complaints. By intervening more quickly on an approaching flare, you will prevent yourself from becoming seriously ill. That greatly improves quality of life.

life. Patients furthermore experienced an easy and effective way of communication with their healthcare providers through myIBDcoach. We believe that broad implementation of telemedicine in parallel with reorganisation of care can further improve long-term disease outcome and thereby patients' quality of life. We had an intensive collaboration with patients during the different phases of this project, and close contact with the patient organisation CCUVN. The fact that we easily included 909 patients in the myIBDcoach trial, underscores that myIBDcoach is of value for IBD patients.

Value for healthcare professionals

Improving quality and value of care is a continuous task for every healthcare professional. To achieve better health outcomes, recent studies show that patients' symptoms and mucosal inflammation need to be tracked closely. Close disease monitoring in a traditional healthcare setting is however challenging due to limited medical and financial resources and more so since the incidence of IBD is increasing. Additionally, due to increasing healthcare costs, healthcare professionals are forced to register disease outcomes and quality parameters increasing the administrative burden. In this regard, telemedicine tools are valuable for monitoring patients at home between outpatient visits and assist healthcare professionals in implementing such a tight control strategy and for automatic registration of quality parameters.

This thesis showed that telemonitoring in combination with patient-tailored information, a personal care plan, and easy, accessible contact with the IBD nurse, resulted in a reduction of healthcare utilisation and hospital admissions and thereby in costs. Additionally, IBD telemanagement creates fast access to healthcare professionals and frees up capacity at the outpatient clinics for those patients with complex disease or in need of urgent action. Furthermore, myIBDcoach focuses on all aspects of this complex disease correlated with the disease course, such as smoking, medication adherence, nutrition or psychological factors. These aspects tend to receive little attention during traditional outpatient visits. Patients using myIBDcoach receive a questionnaire prior to an outpatient visit, including the IBD control questionnaire, which is a sensitive instrument for measuring overall disease control from the patients' perspective, and the "Lastmeter", which is a questionnaire that indicates if there are any inconveniences on physical, emotional, social or practical areas. This together makes the outpatient visit with the gastroenterologist more efficient and patient centered and guarantees that all relevant topics will be discussed and patients will be referred to other specialists whenever necessary. In the MUMC+ we developed a precision medicine model for IBD management, in which care

Gastroenterologist: MyIBDcoach monitors disease activity, but also all different aspects of this complex disease that matter to patients. Such a holistic approach results in more intensive consultations, but it also enriches my work. I believe that tight control and such a holistic approach will improve disease outcomes for IBD on the long-term.

pathways are reorganised with myIBDcoach towards value-based healthcare (see figure 1). After diagnosis, patients start using myIBDcoach and receive immediately adequate education. The follow-up exists of one yearly outpatient visit; in between patients will be telemonitored and mainly managed by specialised IBD-nurses. For each patient, PROMs and patient-reported experience measures (myIBDcoach), classical outcome measures, process indicators and costs (structured registration in hospital information system) are continuously registered and coded. These data are stored in a data-hub and processed to optimise patient-stratification and care pathways for these groups.

Standard care

myIBDcoach

Figure 1. Care pathways with and without myIBDcoach.

Value for society

In addition to more efficient organisation of IBD healthcare, better accessibility of care for IBD patients and a reduction in healthcare costs, this thesis also showed that telemedicine contributes to a reduction in indirect healthcare costs. Due to the early onset and chronicity, IBD profoundly affects work productivity with accompanying economic losses. In the myIBDcoach trial we asked patient to report their hours of sick leave from work and converted these hours into economic losses from a societal perspective, which was €1,886 for myIBDcoach users and €2,058 for patients receiving standard care. Using myIBDcoach, patients only have to visit the hospital when necessary; they can fill out questionnaires at any suitable moment and do not need to ask free from work. In addition, by lowering patients' disease burden and improving patient-empowerment, patients will probably experience less inconvenience of their disease in daily life and work.

In the Netherlands, where around 80,000 patients suffer from IBD, implementation of telemedicine with myIBDcoach would result in a yearly cost saving of 44 million Euro for society. Furthermore, by generating data on quality indicators, telemedicine with myIBDcoach enables benchmarking of IBD clinics and evaluation of practice variation towards better quality of care.

Value for research

MyIBDcoach enables structured registration of PROM data from large patient cohorts. These data can be used for research purposes. Furthermore, myIBDcoach, in combination with at home fecal calprotectin monitoring, is an excellent tool for treatment strategy trials. Currently, several trials are investigating whether de-escalation or episodic administration of biologicals is safe and whether risk factors for recurrence of disease after de-escalation can be identified. In patients who discontinue treatment, close monitoring of disease activity is warranted to enable timely intervention in case of a relapse.

Overall and future value

This thesis showed that telemedicine with myIBDcoach bridges the gap between healthcare workers' requests for tight disease monitoring and continuity of care in an overburdened outpatient setting, patients' demands for more involvement in disease management and more attention to physical, emotional and practical aspects of the disease, and better accessibility of IBD care due to more efficient use of resources. The common benefit for all stakeholders is that implementation of myIBDcoach resulted in better disease outcome with lower costs. These results were needed to help decision makers in estimating the value of telemedicine for IBD. Over the past years this project received much attention (inter)nationally by patients, gastroenterologists, nurses, pharmaceutical industry, governments and insurance companies. Also, people outside the

IBD field were interested. We were invited to present our research at large international congresses and on meetings of decision makers in the Netherlands. This resulted in research prizes, but also in a healthcare innovation award, nomination for the Dutch Value Based HealthCare prize, a nomination as Zinnige Zorg Initiative (Meaningfull Care Initiative) by the insurer VGZ, and the use of myIBDcoach as best practice example by the Federation of Dutch University Medical Centres (NFU)³, by the Dutch Healthcare Authority (NZA)⁴ and by the Dutch Patient Federation. At present, myIBDcoach is used in routine care in 17 hospitals throughout the Netherlands. The optimised myIBDcoach care pathways are shared within this network. Since myIBDcoach will be reimbursed from January 2019, we expect a further adoption of myIBDcoach in the Netherlands. Next, the National Health Service from the United Kingdom, and different hospitals around the world showed their interest in a translated version of myIBDcoach for use in their IBD clinic.

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'Minder opnamen van darmziekte-patiënten dankzij online begeleiding'

<https://www.nu.nl> 15 juli 2017 12:58

De e-health-toepassing MijnIBDcoach, die helpt bij de begeleiding van patiënten met een chronische inflammatoire darmaandoening (IBD) zoals Crohn, blijkt succesvol.

De toepassing zorgt ervoor dat het aantal ziekenhuisopnamen is gehalveerd, er minder polibezoeken plaatsvinden en dat er een betere therapietrouw is. Dat blijkt uit een onderzoek onder bijna duizend patiënten in verschillende Nederlandse ziekenhuizen, onder leiding van het Maastricht UMC+.

MijnIBDcoach laat de patiënt op een interactieve manier over zijn ziekte leren en laat hem of haar communiceren met zijn behandelaar. Die kan op zijn beurt de patiënt op afstand volgen en indien nodig actie ondernemen.

De helft van de onderzoekdeelnemers mocht de toepassing gebruiken. Uit het onderzoek (zaterdag gepubliceerd in het wetenschappelijke tijdschrift *The Lancet*) blijkt dat het aantal patiënten dat in het ziekenhuis opgenomen moest worden, met 50 procent is verlaagd in vergelijking met de groep die de toepassing niet gebruikte.

Wat betreft bezoeken aan de polikliniek is er een afname van 39 procent geconstateerd. Ook zijn patiënten die gebruik maken van de toepassing meer tevreden over de kwaliteit van zorg.

80.000 Nederlanders

Meer dan 80.000 Nederlanders hebben in Nederland last van een chronische darmziekte. De ziekte van Crohn en colitis ulcerosa zijn de twee voornaamste vormen van chronische ontstekingsziekten van de darm.

"Dit bewijst de meerwaarde en potentie van e-health toepassingen voor het efficiënter inrichten van de zorg", aldus maag-, darm-, leverarts Marieke Pierik.

"De tool levert dus een waardevolle bijdrage aan de zorg voor patiënten met een chronische darmaandoening. Willen we de kosten in de toekomst beheersbaar blijven houden, dan zijn structurele veranderingen in de zorg nodig. E-health toepassingen, zoals MijnIBDcoach, zijn uitermate geschikt om het primaire zorgproces efficiënter in te richten, zonder het belang en de behoeften van de patiënt uit het oog te verliezen."

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MJ de Jong, AE van der Meulen-de Jong, MJ Romberg-Camps, MC Becx, JP Maljaars, M Cilissen, AA van Bodegraven, N Mahmmoud, T Markus, WM Hameeteman, G Dijkstra, AAM Masclee, A Boonen, B Winkens, A van Tubergen, DM Jonkers, MJ Pierik. Telemedicine for management of inflammatory bowel disease (myIBDcoach): a pragmatic, multicentre, randomised controlled trial.

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Falk symposium, Madrid, Spain, 2017 [oral presentation].

NVGE, Veldhoven, the Netherlands, 2017 [oral presentation]

Wetenschapsdag Interne Geneeskunde, Maastricht, the Netherlands, 2017 [oral presentation]

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MJ de Jong, A van Tubergen, A Peters, AAM Masclee, V Verstraeten, MJ Pierik. A feasibility study with the telemedicine tool myBiologicalcoach in The Netherlands.

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MJ de Jong, JHRJ Degens, TRA van den Heuvel, M Romberg – Camps, B Winkens, T Markus, AAM Masclee, A van Tubergen, DMAE Jonkers, MJ Pierik. Validation of a patient-reported score to screen for mucosal inflammation in inflammatory bowel disease.

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MJ de Jong, AE van der Meulen-de Jong, M Romberg-Camps, J Degens, M Becx, T Markus, H Tomlow, M Cilissen, N Ipenburg, M Verwey, L Colautti-Duijsens, W Hameeteman, AAM Masclee, DMAE Jonkers, MJ Pierik. Development and feasibility study of a telemedicine tool for all IBD patients: myIBDcoach.

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AWARDS

2016	Best oral presentation wetenschappelijk symposium AtriumMC
2017	Young ECCO abstract award
2017	Best oral presentation Falk Symposium
2017	Takeda Young-ICC research award, 2 ^e prijs
2017	Wetenschapsdag Interne Geneeskunde, beste publicatie 2017
2018	UEGW travel grant

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Liefs Marin

CURRICULUM VITAE

Marin Joanne de Jong was born on May 21st 1988 in Wageningen, the Netherlands. After graduating high school (Pantarijn Gymnasium, Wageningen), she studied medicine at the University of Maastricht. During her master, she did her internship ophthalmology at Kasturba Medical College in Manipal, India and her internship pediatrics at Universidad de La Sabana in Bogotá, Colombia. After acquiring her Medical Doctor's degree, she started working as a resident (ANIOS) at the department of internal medicine at the Gelderse Vallei, Ede. In 2013, she started with the research project described in this thesis: "The PROMise of remote monitoring to improve quality of care for inflammatory bowel disease", supervised by dr. Marieke Pierik, dr. Astrid van Tubergen and prof. dr. Ad Masclee at the Maastricht University Medical Centre, Maastricht. During this project, she had the opportunity to present her work on several international conferences and to publish manuscripts in international peer reviewed medical journals. As of July 2017, she started her gastroenterology training at Leiden University Medical Centre and Haga Hospital in The Hague.