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**Identification of areas of functioning and disability addressed in
inflammatory bowel disease-specific patient reported outcome
measures**

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Summary

Inflammatory Bowel Disease (IBD) is a chronic disabling disease of the gastrointestinal tract. The disease is strongly associated with limited performance of everyday activities and restrictions in work and employment, recreation and relationships to others, as well as reduced quality of life. Thus, suffering from IBD includes not only impairments of body functions and body structures but also limitations of activities in everyday life and restrictions in participation. Consequentially, a comprehensive approach of functioning and disability is required when addressing the impact of IBD.

There are a large number of outcome measures that assess health status problems of persons with IBD. Many of these measures used in clinical practice or research are classification or scoring systems that refer to disease activity and symptomatology in IBD in terms of impaired body functions and structures (e.g., Crohn's Disease Activity Index (CDAI), Harvey Bradshaw Index). Hence, disability and functioning from a comprehensive point of view are poorly addressed in these measures and do not cover the whole spectrum of problems persons with IBD have to deal with. Patient-reported outcome measures (PROMs) offer the possibility to assess health status problems from the perspective of persons suffering a disease. The number of IBD-specific PROMs which focus on aspects of functioning, disability and health (e.g., Inflammatory Bowel Disease Questionnaire (IBDQ-32), Rating Form of IBD Patient Concerns (RFIPC), Inflammatory Bowel Disease Stress Index (IBDSI)) has increased over the last years so that the selection of appropriate PROMs for specific purposes or subpopulations has become a challenge for clinicians and researchers. However, up to now it remains unclear whether currently used IBD-specific PROMs cover the whole spectrum of functioning and disability.

This doctoral thesis examines the content of IBD-specific PROMs using the International Classification of Functioning, Disability and Health (ICF) as a reference to facilitate the selection of appropriate PROMs by clinicians and researchers. The ICF endorsed by the World Health Organization as a common language of functioning and disability is a proven and useful tool for the examination and comparison of the content of outcome measures.

A systematic literature review was performed to identify IBD-specific PROMs used in studies involving persons with IBD. Searches were performed in the literature databases Medline®, EMBASE, PsycINFO, CINAHL and CENTRAL. Searches were limited to English articles published between 1999 and 2009. Eligibility checks of abstracts and full-texts were performed applying pre-defined inclusion and exclusion criteria. IBD-specific PROMs reported in the selected studies, as well as study-related characteristics, were extracted. The items of the identified PROMs were translated (“linked”) to the most specific ICF category according to standardized and established linking rules. The linked ICF categories provided the basis of the descriptive analysis and the comparison of the content of the different PROMs presented in this thesis.

A total of 9,728 papers were identified by the searches in the five electronic databases. The randomly selected abstracts of 2,579 papers were checked on inclusion and exclusion criteria according to the defined eligibility criteria. Based on this abstract check, 221 studies were identified for further analysis. Screening these 221 full-text articles, 46 studies were finally selected that reported the use of IBD-specific PROMs. The following eight IBD-specific PROMs were identified: Cleveland Global Quality of Life (Fazio Score) (CGQL), Inflammatory Bowel Disease Quality of Life Questionnaire (IBDQOL), IBDQ-32, IBDSI, Inflammatory Bowel Disease Questionnaire – short form (IBDQ-9), RFIPC, Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and Work Productivity and Activity Impairment: Crohn’s Disease (WPAI:CD). In total, these eight IBD-specific PROMs included 129 items which were linked to ICF categories. The most frequently identified ICF categories are 'b1300 Energy level' and 'b5254 Flatulence' (IBDQOL, IBDQ-32, IBDQ-9, RFIPC and SIBDQ), as well as 'd920 Recreation and leisure' (IBDQOL, IBDQ-32, IBDSI, IBS-QOL and SIBDQ). Most of the analyzed questionnaires do not cover a wide range of aspects needed to assess functioning and disability from a comprehensive perspective; they only focus on selected aspects of functioning and disability of persons with IBD (e.g., emotional functions, pain, intimate relationships and remunerative employment).

This doctoral thesis provides an item-based examination of the content of IBD-specific PROMs using the ICF as a reference. It offers a clear and precise picture of the addressed PROMs and their contents and enable physicians and

researchers a direct comparison of these contents. The ICF was established as a useful framework for examining and comparing IBD-specific PROMs and their items with respect to the areas of functioning and disability covered. This information can be useful in selecting PROMs for clinical practice, as well as for any kind of investigations in which functioning and disability of persons with IBD is a relevant study outcome.

Zusammenfassung

Chronisch entzündliche Darmerkrankungen (CED) sind eine stark beeinträchtigende Erkrankung des Gastrointestinaltrakts. Patienten, die an dieser Erkrankung leiden, sind nicht nur in ihrem Alltag, sondern auch hinsichtlich beruflicher Aktivitäten als auch in ihren Freizeitbeschäftigungen und in ihrem Sozialleben eingeschränkt. CED gehen somit nicht nur mit Schädigungen von Körperstrukturen und Beeinträchtigungen von Körperfunktionen einher, sondern auch mit Einschränkungen im Alltag und in der sozialen Teilhabe. Daher ist ein umfassender Ansatz notwendig, um die Auswirkung von CED adäquat erfassen zu können.

Es gibt eine Reihe von Erhebungsinstrumenten, mit denen das Outcome bzw. der Gesundheitszustand von Patienten mit CED bestimmt werden kann. Die meisten dieser Instrumente, die in Klinik oder Forschung herangezogen werden, sind Klassifikations- oder Scoringsysteme, die die Schwere der Erkrankung und die entsprechenden Symptome im Sinne von funktionellen Beeinträchtigungen messen (z.B. Crohn's Disease Activity Index (CDAI), Harvey Bradshaw Index). Eine umfassende Krankheitsauffassung und -perspektive kommt in solchen Instrumenten nicht zum Tragen und kann somit nicht das ganze Spektrum von Problemen, mit denen CED-Patienten konfrontiert werden, aufzeigen. Patientenfragebögen dagegen bieten die Möglichkeit, eine Erkrankung aus der Sicht eines Betroffenen einzuschätzen und zu beurteilen. Die Zahl der CED-spezifischen Patientenfragebögen, die sich auf Aspekte wie Funktionsfähigkeit und Gesundheit konzentrieren (z.B. Inflammatory Bowel Disease Questionnaire (IBDQ-32), Rating Form of IBD Patient Concerns (RFIPC), Inflammatory Bowel Disease Stress Index (IBDSI)) hat in den letzten Jahren stark zugenommen, so dass die Auswahl von adäquaten patientenbezogenen Messinstrumenten für spezifische Fragestellungen eine Herausforderung für Kliniker und Wissenschaftler darstellt. Es wurde bisher noch nicht untersucht, welches dieser patientenbezogenen Messinstrumente das ganze Spektrum von Funktionsfähigkeit und Gesundheit abdeckt.

Diese Dissertation untersucht den Inhalt von CED-spezifischen Patientenfragebögen. Die Internationale Klassifikation der Funktionsfähigkeit,

Behinderung und Gesundheit (ICF) dient hierbei als Grundlage, um einen Überblick über die Inhalte der Fragebögen zu ermöglichen und somit die Auswahl für Kliniker und Wissenschaftler zu erleichtern. Die ICF, ein Klassifikationssystem der Weltgesundheitsorganisation (WHO) zur Beschreibung von Funktionsfähigkeit und Gesundheit, ist ein etabliertes und nützliches Instrument, um den Inhalt von Messinstrumenten zu untersuchen und zu vergleichen.

Mittels eines systematischen Literaturreviews wurden CED-spezifische Patientenfragebögen bestimmt, die in CED-Studien verwendet wurden. Die Suche wurde in folgenden Datenbanken durchgeführt: Medline®, EMBASE, PsycINFO, CINAHL und CENTRAL. Die Suche wurde beschränkt auf Studien in englischer Sprache, die zwischen 1999 und 2009 veröffentlicht wurden. Abstrakts und Volltexte wurden anhand von zuvor festgelegter Auswahlkriterien gescreent. CED-spezifische Fragebögen, die in den eingeschlossenen Studien verwendet wurden, und studienbezogene Charakteristika wurden identifiziert und dokumentiert. Die Items der identifizierten Fragebögen wurden in die Sprache der ICF übersetzt, d.h. zu ICF-Kategorien gelinkt. Dieses Linking der Fragebogen-Items wurde gemäß standardisierter und etablierter Richtlinien vorgenommen. Die gelinkten ICF-Kategorien bildeten die Basis der in dieser Dissertation beschriebenen Analyse und dem Inhaltsvergleich der verschiedenen CED-spezifischen Patientenfragebögen.

Insgesamt wurden 9728 Studien durch Suche in den fünf elektronischen Datenbanken identifiziert. Nach Ziehung einer Zufallsstichprobe wurden 2579 Studien nach zuvor definierter Auswahlkriterien auf ihre Ein- bzw. Ausschlusskriterien hin geprüft. Nach Lesen der Abstracts verblieben 221 Studien, die inhaltlich einer genaueren Untersuchung bedurften. Ausgehend von diesen 221 Studien wurden schließlich 46 selektiert, bei denen die Verwendung von CED-spezifischen Patientenfragebögen berichtet wurde. In diesen Studien wurden folgende acht Instrumente benannt: Cleveland Global Quality of Life (Fazio Score) (CGQL), inflammatory Bowel Disease Quality of Life Questionnaire (IBDQOL), IBDQ32, IBDSI, Inflammatory Bowel Disease Questionnaire – Kurzversion (IBDQ-9), RFIPC, Short Inflammatory Bowel Disease Questionnaire (SIBDQ) and Work Productivity and Activity Impairment: Crohn's Disease (WPAI:CD). Insgesamt enthalten diese acht CED-spezifischen Fragebögen 129

Items, die zur ICF gelinkt werden konnten. Folgende ICF-Kategorien wurden in den untersuchten Fragebögen am häufigsten identifiziert: 'b1300 Ausmaß der psychischen Energie' und 'b5254 Flatulenz' (IBDQOL, IBDQ-32, IBDQ-9, RFIPC and SIBDQ) sowie 'd920 Erholung und Freizeit' (IBDQOL, IBDQ-32, IBDSI, IBS-QOL and SIBDQ). Die meisten Fragebögen decken allerdings kein breites Spektrum an Aspekten ab, die notwendig sind, um Funktionsfähigkeit von einer umfassenden Perspektive aus zu beschreiben, sie fokussieren dagegen nur auf einzelne Aspekte von Funktionsfähigkeit, wie z.B. emotionale Funktionen, Schmerz, intime Beziehungen und Erwerbstätigkeit.

Die vorliegende Doktorarbeit berichtet über eine Item-basierte Inhaltsanalyse von CED-spezifischen Patientenfragebögen unter Verwendung der Sprache der ICF-Klassifikation. Sie bietet eine präzise Beschreibung der analysierten Fragebögen und deren Inhalte und ermöglicht somit Klinikern und Wissenschaftlern einen direkten Vergleich der Inhalte der verschiedenen Fragebögen. Die ICF diene hierbei als ein nützliches Rahmenkonzept, um die Untersuchung und den Inhaltsvergleich der CED-spezifischen patientenbezogenen Fragebögen und deren Items hinsichtlich der Bereiche Funktionsfähigkeit und Gesundheit vorzunehmen. Diese Informationen können bei der Auswahl von Patientenfragebögen für die klinische Praxis als auch für Untersuchungen und Studien der unterschiedlichsten Art, bei der die Erfassung von Funktionsfähigkeit und Gesundheit von CED-Patienten ein Studienoutcome darstellt, von großem Nutzen sein.

1. Introduction

1.1 Inflammatory Bowel Diseases¹

Inflammatory Bowel Disease (IBD) is a chronic disabling disease of the gastrointestinal tract.^{1,2} The most common entities are Crohn's disease and ulcerative colitis with symptoms like diarrhea, rectal urgency, abdominal discomfort and weakness.^{3,4} Symptoms may not be limited to the intestine but can also have extraintestinal manifestations affecting e.g. the skin, joints and eyes.⁵

1.1.1 Prevalence and pathophysiology of inflammatory bowel disease

Countries of the northern hemisphere like Europe and the United States have the highest prevalence with 44 patients per 100 000. Countries of the southern hemisphere like Asia and Africa have a much lower prevalence of 4 per 100 000.⁶ When people migrate to more northern and developed countries they are subject to the local incidence rates. Crohn's disease is more often diagnosed in Jewish people with ulcerative colitis being three to five times more prevalent.⁷

A positive family history is the largest independent risk factor for the disease. The estimated lifetime risk of developing IBD for a first degree relative is between 4.8% and 5.2%.⁸ A German nationwide study about the epidemiology of IBD shows that in monozygotic twins 35% were concordant for Crohn's disease and 16% for ulcerative colitis. In dizygotic pairs 3% with Crohn's disease and 2% dizygotic twins with UC were concordant for the disease.⁹ Ulcerative colitis and Crohn's disease are polygenic and have susceptibility regions on 12 different chromosomes. Some of them have been renamed IBD 1-9. Chromosome 6 (IBD3) has been linked to all IBDs regardless of the geographic location of the person. More specific gene locations with an array of polymorphisms have been identified on chromosome 16 as CARD15 (NOD2). This location is exclusively associated with Crohn's disease in white populations.

¹ The information about IBD derive mainly from Baumgart D et al (6) and Mayer E, Irritable Bowel Syndrome, N Engl J Med 2008; 358; 1692-1699 and Baumgart D et al. (41)

As the prevalence is so different between countries of the northern and southern hemisphere a major focus has been directed to differences in life style. Breastfeeding, the consumption of carbohydrates and the intake of polyunsaturated fats or margarine have been implicated. But so far no final conclusions about the role of nutrition in IBD can be made. As there is a low incidence of IBD in developing countries it has been suggested that excessive sanitation might limit exposure to environmental antigens and might impair the maturation of the mucosal immune system. This may result in inappropriate immune responses when re-exposed to these antigens later in lifetime. In addition, chronic stress and depression may increase the probability in patients with dormant disease. Although IBD is more common after gastrointestinal infection, no specific causative agent has so far been identified. This emphasizes the notion that the basic problem of IBD is an impaired handling of microbial antigens by the intestinal immune system.

In the normal gut there is an epithelial barrier that consists of a polarised single layers covered with mucus that contains secretory IgA and glycocalyx. Fluxes through the intestinal epithelium proceed through a transcellular route. Antigen recognition and immune regulation are mediated via a family of the toll like receptors. Toll like receptors trigger antimicrobial responses that lead to activation of nuclear transcription factors and induction of the inflammatory cytokine cascade. This may be the reasons why prolonged non-steroidal anti-inflammatory drugs (NSAID) use but not aspirin intake is associated with an increased risk for IBD¹⁰. The gut mucosa also includes lymphoid tissue with T cells, B cells, granulocytes, mast cells, natural killer cells and natural killer T-cells which are located in the lamina propria. Antigens and microbes are channelled through the epithelial barrier to those lymphoid cells, where they meet dendritic cells and macrophages. Dendritic cells are able to differentiate in their response between pathogens and normal intestinal flora by expressing the entire spectrum of toll like receptors.

The defective mucosal immune system in IBD results in an inappropriate response to the normal gut flora. Experimental and clinical evidence suggests the following mechanisms:

- (1) T-cell mediated disruption of tight junction protein as well as enteric neuron dysfunction may increase gut permeability. This may precede the clinical onset of disease and be associated with a CARDIS15 3020insC mutation.
- (2) Patients with IBD have different expression of toll like receptors. TLR 3 is significantly downregulated in Crohn's disease; TLR4 is upregulated in Crohn's disease and ulcerative colitis.
- (3) Antigen recognition by dendritic cells is disturbed. Dendritic cells incorrectly recognize normal gut bacteria and induce a proinflammatory immune response normally directed at pathogens.
- (4) Atypical antigen-presenting cells may become potent T-cell activators in patients with inflammatory bowel disease. It has been demonstrated in patients with IBD that intestinal-epithelial cells might be transformed into functional antigen-presenting cells.
- (5) Patients with Crohn's disease have an altered clearance of over-reactive T-cell populations thus fuelling the inflammatory process.
- (6) In Crohn's disease the balance of regulatory and effector cells is disturbed which perpetuates inflammation.
- (7) In patients with IBD psychosocial stress might trigger the inflammatory cascade through neuroimmunological interaction by shifting the balance of the autonomic nervous system. Whereas the vagus has a substantial inhibitory effect and attenuation of the systemic inflammatory response, the activation of the sympathetic system in ulcerative colitis can cause an increased colonic paracellular permeability.

As a result of these mechanisms there is migration of inflammatory cells from the capillaries into the intestinal mucosa. Proinflammatory cytokines (IL 1, TNF alpha) upregulate the expression of adhesion molecules ligands on the vascular endothelium of the mucosal blood vessels promoting leukocyte adhesion and extravasation into the tissue.^{11,12} In this way, a multitude of aggressive metabolites

and mediators accumulate in the mucosa resulting in tissue damage. A vast array of mediators promotes fibroblast growth with collagen secretion and stricture formation. To terminate or prevent the initiation and perpetuation of the inflammatory cascade a specific approach aimed at the above mentioned mechanism is needed.

1.1.2 Clinical aspects

Ulcerative colitis

Ulcerative colitis is a recurrent non-transmural inflammatory disease that is restricted to the colon. Proctitis, left-sided colitis or pancolitis can occur. Ulcerative colitis is a clinical diagnosis confirmed by objective findings from endoscopic and histological examinations. The disease is typically described as mild (up to four bloody stools per day), moderate (four to six bloody stools per day) or severe (more than six bloody stools as well as fever, tachycardia and anaemia). The final stage is a fulminant colitis with more than ten stools, continuous bleeding, abdominal tenderness and colonic dilation progressing to toxic megacolon. The disease is characterized by alternating relapses and remissions. Overall, patients with ulcerative colitis have a normal life expectancy.

Crohn's disease

Crohn's disease is a relapsing, transmural inflammatory disease of the gastrointestinal mucosa that can affect the entire gastrointestinal tract from the mouth to the anus. Complications include strictures, abscesses or fistulas. At diagnosis, the disease is located in the terminal ileum in 47%, the colon in 28%, the ileocolon in 21% and the upper gastrointestinal tract in 3%. The clinical presentation is dependent on disease location and can include diarrhoea, abdominal pain, fever, bowel obstruction, as well as passage of blood or mucus or both.

There is no definitive diagnostic test for Crohn's disease. The disease activity is described as mild to moderate (patient tolerating oral food), moderate to severe (fever, weight loss, abdominal pain, anaemia) and severe to fulminant (high fevers, vomiting, intestinal obstruction, cachexia, abscess). In the course of the disease the anatomical location is stable, but it may change from non-stricturing to either stricturing (27%) or penetrating (29%) disease. After 20 years most patients with Crohn's disease will require surgery. The life expectancy is slightly reduced.

Complications and manifestations in Crohn's disease and ulcerative colitis

In addition, there are neoplastic complications of IBD including colon cancer in patients with ulcerative colitis and Crohn's disease. A screening colonoscopy with multiple biopsies is indicated 8 to 10 years after onset of ulcerative colitis, decreasing the interval to 1 to 2 years in patients with extensive disease. After 20 years of onset, yearly controls are recommended. Patients with primary sclerosing cholangitis have an increased risk of developing colorectal cancer and should be checked on a yearly basis. Colectomy is indicated in patients with ulcerative colitis with high-grade dysplasia or evidence of colorectal cancer. In patients with Crohn's disease the risk of colorectal cancer is similar to that for ulcerative colitis.

Furthermore, there is to mention that there are also extraintestinal manifestations of IBD. They include in the head area uveitis, episcleritis and sensorineural hearing loss and in the trunk area pleuritis, myocarditis, sclerosing cholangitis, nephrolithiasis, pancreatitis, ankylosing spondylitis and sacroileitis. In the extremities arthritis, erythema nodosum, pyoderma gangrenosum and tendinitis can be observed. Overall, patients with IBD have a higher risk of venous thromboembolism (2.6 per 1000 person-years).¹³ At the time of a flare, this increase in risk is much more prominent (9.0 per 1000 person-years).¹³ Thus, trials of primary prophylaxis of venous thromboembolism are warranted to find out whether this important complication can be prevented.¹³

Abdominal pain is a common symptom of IBD. Pain may arise from different mechanisms like partial blockade and gut distention, as well as severe intestinal inflammation. Even without acute flare a significant percentage of patients

continue to experience pain. Current evidence suggests that sensory pathways sensitize during inflammation, leading to persistent changes in afferent neurons and central nervous system pain processing. Pain processing and the activation of sensory pathways are modulated by arousal, emotion, and cognitive factors. Considering the high prevalence of iatrogenic as well as neuropsychiatric comorbidities, these central modulating factors may significantly contribute to the clinical manifestation of chronic pain.

Differential diagnosis: IBD versus inflammatory bowel syndrome (IBS)

IBD has to be separated from IBS which is characterized by chronically recurring abdominal pain or discomfort and altered bowel habits. It is much more common with a worldwide prevalence of 10-15%.¹⁴ In the absence of detectable organic causes, IBS is referred to as a functional disorder, which is defined by symptom-based diagnostic criteria known as the “Rome criteria”. IBS-like symptoms develop in approximately 10% of adult patients after bacterial or viral enteric infections. Risk factors for the development of post-infectious IBS include female sex, a longer duration of gastroenteritis and the presence of psychosocial factors like major life stress at the time of infection and somatization. Thus, IBS is often described as a “brain-gut disorder”. Its pathophysiology remains uncertain. Dysregulation of the gut-based serotonin signaling system, alterations in immune activation of the mucosa and intestinal microflora may contribute to symptoms of IBS. Some of these symptoms may be similar to celiac sprue, microscopic and collagenous colitis and atypical Crohn’s disease.

1.1.3. Functioning and health in IBD

The disease is strongly associated with limited performance of every-day activities and restrictions in work and employment, recreation activities and relationships with others. Rubin et al. showed that patients with ulcerative colitis found living with their disease to be a daily struggle (61%), more so than patients with asthma (33%) or migraine headaches (45%).¹⁵ A significantly greater proportion of patients with ulcerative colitis (60%) reported that their disease had ruined (‘wrecked’) important moments of their lives compared to patients with asthma (25%) or

rheumatoid arthritis (48%). More patients with ulcerative colitis felt that their disease was controlling their lives (53%) than patients with any of the other surveyed diseases. Furthermore, patients with ulcerative colitis reported that their disease caused difficulties with travel and participation in recreational activities or public events.¹⁵ With regard to impact of every-day activities, three times the number of IBD patients reported having reduced activity (often or sometimes) at work and at home compared to a non-IBD community sample. Half of those with IBD reported significantly greater interference in other activities as well. Even those with inactive IBD reported significantly greater interference (reduction of activity) across several domains compared to the (non-IBD) community sample.¹⁶ Muller et al. showed that a very large proportion of patients with IBD perceive a negative impact of their disease on many aspects of their sexuality. Specifically, female gender and surgery for IBD are risk factors for a negative view of body image, libido and frequency of sexual activity. In addition, 88.5 percent of IBD patients reported that their quality of life was impaired by IBD.⁴⁵ Thus, suffering from IBD includes not only impairment of body functions and structures but also limitations in activities of every-day activities and restrictions in participation.

1.1.4. Treatment

Treatment of ulcerative colitis

First-line therapy for patients with mild to moderate ulcerative colitis is 5-aminosalicylic acid as rectal and oral drugs. Doses of 1500-2400 mg per day of oral 5-aminosalicylic acid will be effective in most patients. Proctitis and left-sided ulcerative colitis might respond better to rectal mesalazine or corticosteroids. Patients who do not respond to oral or rectal therapy should be treated with oral corticosteroids. In difficult cases infliximab, a chimeric monoclonal antibody to tumour-necrosis factor (TNF) can be tried.

First-line therapy for the maintenance of remission is oral mesalazine with a minimal oral dose of 1500 mg per day. Further options are ciclosporin, azathioprine and mercaptopurine.

Surgical management is indicated in patients with bowel perforation, refractory rectal bleeding and toxic megacolon not responsive to medical management. The accepted surgical technique is total proctocolectomy with ileal J-pouch-anal anastomosis.

Treatment of Crohn's disease

First-line therapy for patients with mild to moderate Crohn's disease is sulfasalazine at doses of 3000-4500 mg per day. Mesalazine did not show a clinically important treatment effect. The corticosteroid budesonide is given orally or via rectum. Its extensive first-pass hepatic metabolism markedly reduces systemic side-effects of this corticosteroid. A 9 mg per day dose budesonide is more effective than 4000mg per day oral 5-aminosalicylic acid and has similar efficacy to prednisolone in active Crohn's disease.¹⁷ Antibiotics failed to show efficacy for induction of remission. Thus, sulfasalazine can be recommended for induction therapy in patients with mildly to moderately active disease with colonic involvement and budesonide in patients with ileal or right colonic involvement or both. Patients who do not respond are treated with oral prednisone 40 mg per day. About 44% of patients with Crohn's disease need corticosteroids to achieve remission. When these treatments fail monoclonal antibodies to TNF like infliximab or adalimumab can be tried.

For maintenance of remission 5-aminosalicylic acid, azathioprine, mercaptopurine or methotrexate are used. Because of the slow onset of these drugs they are mainly used as maintenance rather than induction agents. These drugs should generally be combined with fast-acting drugs like budesonide, conventional steroids and/or infliximab. The latter is effective for maintenance of remission, steroid sparing and mucosal healing in patients who are unable to maintain remission with the other drugs.

For management of fistulas in patients with Crohn's disease antibiotic therapy with

ciprofloxacin 1000 mg per day or metronidazole is the first-line treatment. In addition, azathioprine or mercaptopurine are used as a second-line treatment. When these therapies fail, infliximab or adalimumab can be added.

Indications for surgery include formation of strictures leading to bowel obstruction, internal fistulas complicated by abdominal abscess formation, as well as endovesical and/or entrocuteaneous fistulas.

Future therapies for IBD

Future therapies for IBD include:

- (1) the blockade of TNF by infliximab, adalimumab and certilizumab and possibly etanercept;
- (2) The modulation of other key cytokines by the humanised interferon-gamma antibody fontolizumab;
- (3) The blockade of T cells by the humanised anti-CD3 antibody visilizumab;
- (4) The blockade of inflammatory cell migration and adhesion by the alpha 4-integrin natalizumab.

Many of the new therapies for IBD using immunosuppressants and -modulators are associated with potentially severe side effects ranging from cutaneous and pulmonary hypersensitivities (pneumonitis), bone marrow depression, hepatic disease to demyelination, drug-induced lupus, heart failure serious infections, non-Hodgkin`s lymphoma and solid tumour malignancies.

1.2 Outcome measures in IBD

There are a large number of outcome measures assessing health-status problems of persons with Crohn's disease or ulcerative colitis.¹⁸ Many of these measures used in clinical practice or research are classification or scoring systems that refer to disease activity and symptomatology in IBD in terms of impaired body functions and structures. The Crohn's Disease Activity Index (CDAI)¹⁹ for example is a measurement to quantify the symptoms of patients with Crohn's disease. The

questionnaire includes components as the number of liquid or soft stools per day, abdominal pain or the number of complications. The CDAI is focused on the symptoms of Crohn's disease, so does the Harvey Bradshaw Index²⁰, another often used measurement to quantify the symptoms of Crohn's disease. The Harvey Bradshaw Index is also concentrated on clinical symptoms (number of liquid stool, abdominal pain, abdominal mass). The Truelove and Witts Severity Index²¹ is another established measurement to assess the disease activity, composed of six variables as blood in stool, temperature, pulse, haemoglobin and erythrocyte sedimentation rate.

The CDAI has been used to measure Crohn's activity for many decades. The development of the CDAI is reviewed and its reliability and validity are examined. Instruments used to assess Crohn's disease that were developed subsequent to the CDAI, including the Harvey-Bradshaw Index, are similarly reviewed.²² In these measurements disability and functioning from a comprehensive point of view are poorly addressed and do not cover the whole spectrum of problems persons with IBD have to deal with.^{23,24}

Patient-reported outcome measures (PROMs) provide the possibility to assess health-status problems from the perspective of persons suffering from a disease. The number of IBD-specific PROMs which focus on aspects of functioning, disability and health (e.g. Inflammatory Bowel Disease Questionnaire (IBDQ-32),²⁵ Rating Form of IBD Patient Concerns (RFIPC),²⁶ Inflammatory Bowel Disease Stress Index (IBDSI)²⁷) has increased over the last years so that the selection of the appropriate PROMs for specific purposes or subpopulations has become a challenge. However, up to now it has remained unclear whether these PROMs cover the whole spectrum of functioning and disability.

1.3 The International Classification of Functioning, Disability and Health

A comprehensive, efficient treatment for patients requires an interdisciplinary collaboration between the involved health professionals and other relevant instances. To assure the most efficient collaboration a common language for describing health and health-related states which can be used and understood by all parties is needed. The International Classification of Functioning, Disability and Health (ICF) provides such an unified and standard language²⁸. Since its approval in May 2001 by the fifty-fourth World Health Assembly (WHA), which is a member of the WHO family of International Classification, all member states of the World Health Organization (WHO) are urged to implement the ICF in clinical practice. The ICF establishes a universal and generally accepted language for the description of health conditions and health-related states and a globally agreed-upon framework for all health professionals as well as researchers, policy makers and the public.²⁸

The ICF is based on an integrative and functional model of health that provides a holistic, multidimensional and interdisciplinary understanding of health and health-related states. It is divided into two parts: *Functioning and Disability* and *Contextual Factors*. According to the ICF *Functioning and Disability* refer to the ICF components Body Functions, Body Structures and Activities & Participation in life situations. Body Functions are defined as physiological and psychological functions of the body system whereas Body Structures contain the anatomical structures of the body like organs, limbs and their components. The component Activities & Participation includes all domains which are associated with the aspects of functioning from individual and societal perspective. Activity means the execution of something and participation the involvement in situations. The components of the part Functioning and Disability can be used to describe problems of patients like impairments of Body Functions and Body Structures, limitations of Activities and restrictions of Participation as well as to describe non-problematic aspects of health and health-related states. In this context, functioning characterizes the positive aspects and disability the negative aspects of the interaction between an individual with a health condition and its contextual factors.

The part *Contextual Factors* includes the components Environmental Factors and Personal Factors (figure1). Environmental Factors can have an impact on all components of *Functioning and Disability* and include the physical, social and attitudinal environment of a person, which can be facilitating or hindering for the individual. *Personal Factors* are e.g. gender, race, age, lifestyle, habits, coping styles, and social background of the individual.

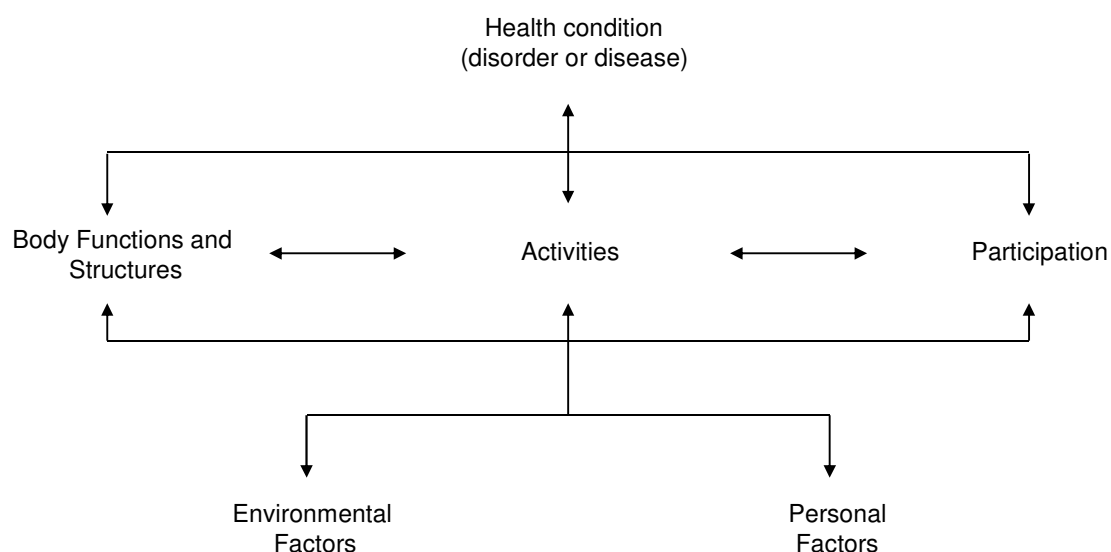


Figure1: Structure of the International Classification of Functioning, Disability and Health

The construction of the ICF is hierarchical. Within each component there is a list of so-called ICF categories which are the units of the classification²⁸. ICF categories are part of chapters which constitute the first level of precision. The categories are denoted by unique alphanumeric codes composed by a letter that refers to the components of the classification (b: *Body Functions*; s: *Body Structures*; d: *Activities & Participation*; e: *Environmental Factors*) and followed by a numeric code starting with the chapter number (one digit), followed by the second level (two digits) and the third and fourth level (one digit each) (figure 2). An example from the component *Body Functions* is as follows:

Component		b	Body functions
Chapter	first level	b 2	Sensory functions and pain
Categories	second level	b 280	Sensation of pain
	third level	b 2801	Pain in body part
	fourth level	b 28015	Pain in lower limb

Within each component the categories are arranged in a stem / branch / leaf scheme. Consequently, a higher-level (more detailed) category shares the lower level category of which it is member. Therefore, when using a higher level category it is possible to apply the lower-level category but not vice versa.

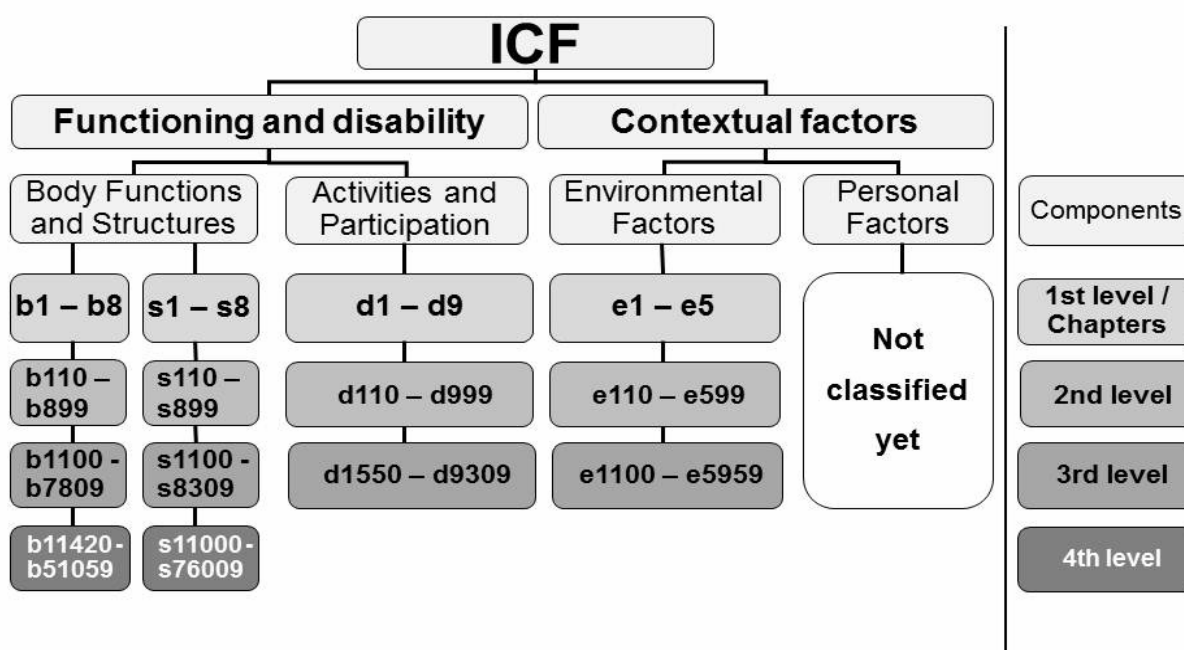


Figure 2: Structure of the International Classification of Functioning, Disability and Health; hierarchical arrangement

Altogether, the ICF contains more than 1400 categories each allotted into the components named above except of the *Personal Factors* which are not yet classified. To facilitate the application of the ICF in clinical practice, the ICF Core Sets project was initiated in 2001 by the ICF Research Branch of the WHO

Collaboration Centre of the Family of International Classifications (DIMDI) at the Ludwig-Maximilians-Universität (LMU) in Munich, Germany, together with the Classification, Terminology and Standards Team (CTS Team) at the WHO and an increasing number of partner organizations²⁹.

IBD is a disabling disease with various limitations in functioning and it is therefore strongly associated with limited performance of every-day activities and a reduced quality of life. To assess the health status of patients with IBD there are a large number of different outcome measures. Hence, disability and functioning from a comprehensive point of view are poorly addressed in most of these measures. However, PROMs offer the possibility to assess health status problems from the perspective of persons suffering a disease from a more comprehensive point of view.

It would be a challenge to describe and examine functioning and disability assessed with PROMS using the ICF as a reference. To our knowledge no overview has been published so far that examines the content of IBD-specific PROMs using the ICF as a reference. Such an overview would facilitate the selection of PROMs by clinicians and researchers.

2. Objective

The objective of this doctoral thesis is to examine the content of IBD-specific PROMs using the ICF as a reference. The specific aims are (1) to identify IBD-specific PROMs applied in studies of persons with IBD based on a systematic literature review of articles published between 1999 and 2009 and (2) to examine which areas of functioning and disability have been addressed by these PROMs using the ICF as a reference.

The study reported in this doctoral thesis has already been published in the *Journal of Crohn's and Colitis*³⁰.

3. Materials and methods

A systematic literature review was performed to identify IBD-specific PROMs used in studies of persons with IBD. In our study, PROMs were defined as outcome measures in which patients respond to a number of standardized questions asked in a paper-pencil form. The items of the identified PROMs were translated ("linked") to the ICF. The linked ICF categories provided the basis of the descriptive analysis and the comparison of the content of the different PROMs is presented in this thesis.

3.1 Systematic literature review: selection of studies

Searches were performed in the literature databases Medline[®], EMBASE, PsycINFO, CINAHL and CENTRAL using the search terms 'Colitis, Ulcerative', 'Crohn Disease', 'Inflammatory Bowel Disease' in MESH terms (if available), title and abstract. Searches were limited to English articles published between 1999 and 2009.

A random sample of about 25% of the abstracts identified in the searches were screened and selected based on the following eligibility criteria (Appendix 1 'eligibility criteria'):

- (1) human population;
- (2) sample size more than 10 study participants;
- (3) age of at least 18 years;
- (4) main diagnoses of Crohn's disease (regional enteritis), Crohn's disease of small intestine, Crohn's disease of large intestine, other Crohn's disease, ulcerative colitis, ulcerative (chronic) enterocolitis, ulcerative (chronic) ileocolitis, ulcerative (chronic) proctitis, ulcerative (chronic) rectosigmoiditis, other ulcerative colitis and ulcerative colitis, unspecified;
- (5) application of IBD-specific PROMs.

Studies should present first-hand data concerning persons with IBD irrespective of the type of intervention or setting. In addition, the information in the abstracts was

used to assure the inclusion of randomized controlled trials, clinical controlled trials, cross-sectional studies, and longitudinal observational studies. Reviews or meta-analyses, case reports/case series, primary prevention studies, ecologic studies, economic evaluation studies and decision analyses were excluded. Comments, letters, editorials, guidelines, conference reports, book chapters and dissertations were excluded as well. Screening of abstracts was independently performed by the author of this doctoral thesis and a team member of the ICF Research Branch. Consensus between the two researchers was achieved to decide which abstracts to include. In case of disagreement, pros and cons were discussed and if necessary a third researcher (team member of the ICF Research Branch) was involved to reach consensus and to decide on the inclusion of abstracts.

Full-text articles of the selected studies were retrieved and checked applying the same eligibility criteria as reported above.

3.2 Extraction of the selected studies

The IBD-specific PROMs reported in the selected studies, as well as study-related characteristics specified in the methods and results section (i.e. sample size, age and gender of study participants, main diagnosis, type of intervention), were extracted. Quality and plausibility checks of the data extraction were performed. Data collected in steps 1 and 2 were documented in a Microsoft® Access database. Descriptive statistics were performed to describe the study-related characteristics of the selected studies.

3.3 Linkage of the identified PROMs

The items of the identified IBD-specific PROMs were translated (“linked”) to the ICF. The linkage procedure started with the identification of linking units contained in the items of the PROMs. These linking units were then linked to the most specific ICF category according to established linking rules by two independent

researchers.^{31,32} Those linking units which were not sufficient to make a decision about the most precise ICF category were assigned 'nd' (not definable). If a linking unit was a personal factor as defined in the ICF, it was assigned 'pf'. If a linking unit was not represented by the ICF, the code 'nc' (not covered) was chosen.

Consensus between the two independent researchers (the author of this thesis and a team member of the ICF Research Branch) was achieved to decide which ICF category was to be linked to each linking unit. In case of disagreement, the arguments were discussed and if necessary a third researcher (team member of the ICF Research Branch) was involved to reach consensus and to decide on the final category (Appendix 2 'example of a linked PROM').

Kappa statistics with bootstrapped 95 percent confidence intervals (95% CI) were calculated using SAS for Windows V 9.1 (SAS Institute Inc., Cary, NC, USA) to analyse the agreement between the two researchers who performed the linking.^{33,34} The values of the Kappa coefficient generally range from 0 to 1, whereas 1 indicates perfect agreement and 0 indicates no additional agreement beyond what is expected by chance alone.

3.4 Content comparison of the linked items

Absolute frequencies of the linked ICF categories addressed in the items of the identified IBD-specific PROMs were calculated using the second level of the ICF classification. Therefore, for items linked to a third- or fourth-level ICF category the respective second-level category was considered for analysis. Since the ICF is organized in a hierarchical scheme, more specific third- or fourth-level categories share the attributes of less specific second-level categories.

The steps of this systematic literature review along with their results are presented in Figure 3.

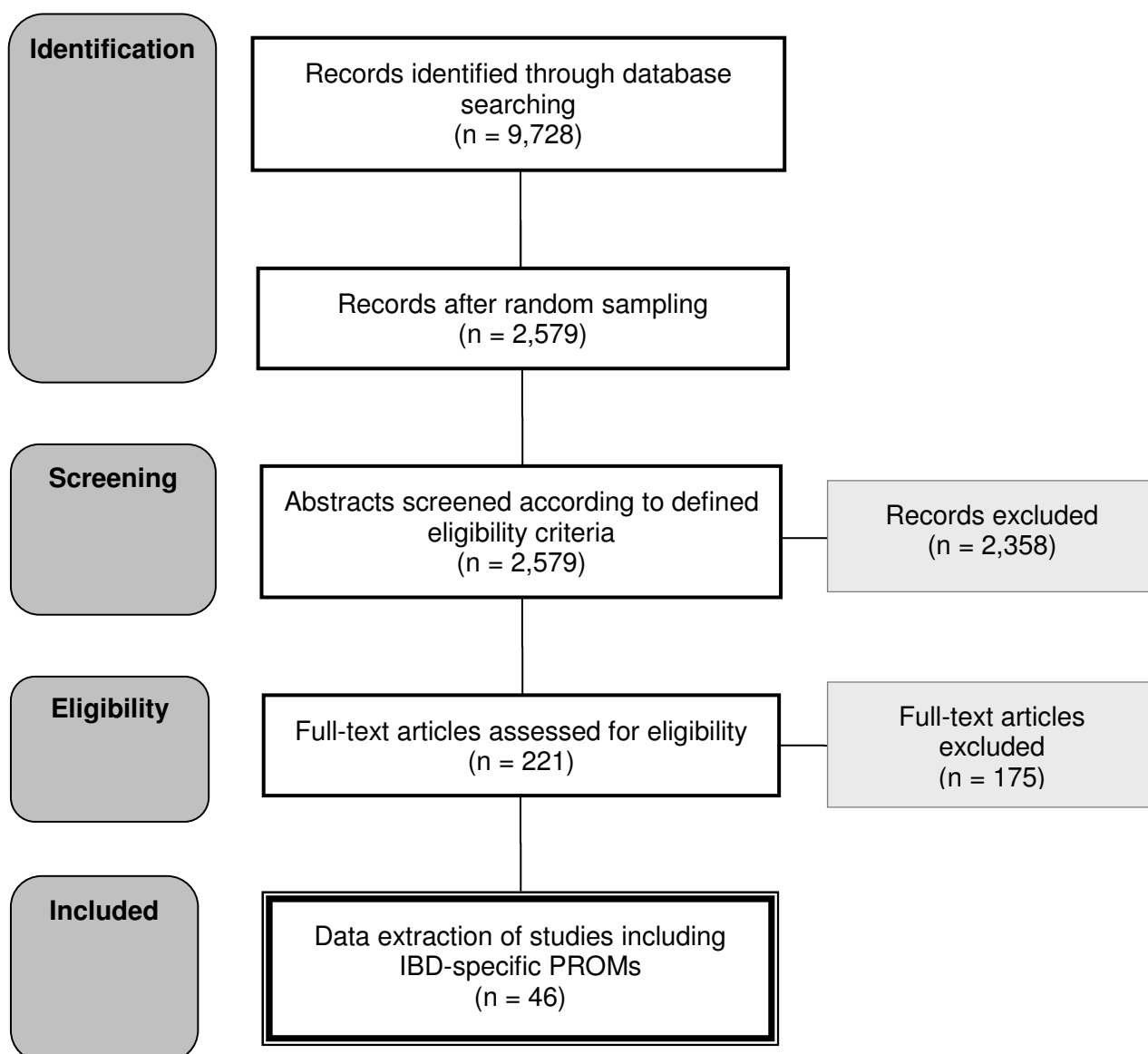


Figure 3: Procedure of the systematic literature review

4. Results

4.1 Systematic literature review: selection of studies

A total of 9,728 papers were identified by the searches in the five electronic databases. The randomly selected abstracts of 2,579 papers were checked on inclusion and exclusion criteria according to the defined eligibility criteria. Based on this abstract check, 221 studies were identified for further analysis. Screening these 221 full-text articles, 46 studies reporting the use of IBD-specific PROMs were finally selected. The main reason for excluding full-text articles was the use of non-IBD specific PROMs (Appendix 3 'List of references of included studies').

4.2 Extraction of the selected studies

Most of the selected studies were pharmaceutical intervention studies (n=19, 41.3%) followed by nine longitudinal descriptive studies (19.6%) and six cross-sectional descriptive studies (13.0%). Two retrospective chart review studies (4.3%) were included, as well as three undefined intervention studies (6.5%), two surgical intervention studies (4.3%) and five psychometric/diagnostic evaluation studies (10.9%).

Nearly half of the identified studies (n=19, 41.3%) included persons with the main diagnosis Crohn's disease. The main diagnosis in 16 studies (34.8%) was ulcerative colitis. Eleven studies (23.9%) included both diagnoses.

There was a total sample size of 9,396 persons ranging from 12 to 1,156 patients in the different individual studies. The total sample included 3,537 females (37.6%, missing data n=5 studies). The mean age of the total sample was 39.5 years (SD=4.3, 18-79 years; data available in 27 studies). Table 1 shows the countries of origin of the included studies.

Table 1 Countries of origin of the identified studies (N=46)

Country of origin	<i>n</i>	%
United States of America	11	23.9
Germany	7	15.2
Spain	6	13.0
United Kingdom	4	8.7
Sweden	4	8.7
Canada	2	4.3
Netherlands	2	4.3
Norway	2	4.3
Other countries	8	17.4

The following eight IBD-specific PROMs were identified in the retrieved studies: Cleveland Global Quality of Life (Fazio Score) (CGQL)³⁵, Inflammatory Bowel Disease Quality of Life Questionnaire (IBDQOL)³⁶, IBDQ-32²⁵, IBDSI²⁷, Inflammatory Bowel Disease Questionnaire – short form (IBDQ-9)^{37,38}, RFIPC²⁶, Short Inflammatory Bowel Disease Questionnaire (SIBDQ)³⁹ and Work Productivity and Activity Impairment: Crohn’s Disease (WPAI:CD)⁴⁰. These PROMs, their major characteristics and the number of the studies which reported their use are shown in Table 2.

Table 2 Characteristics and frequencies of the identified IBD-specific PROMs in the included studies (N=46)

PROMs		Frequency <i>n</i> (%) ^a	Aim	Mode of administration	Number of items	Response options	Time frame	Languages
CGQL	Cleveland Global Quality of Life (Faszio Score) ²⁶	1 (1.7)	Quality of life after pelvicpouch surgery	Self, Interviewer	3	Rating 0 - 10	Today ^b	English
IBDQOL	Inflammatory Bowel Disease Quality of Life Questionnaire ²⁷	6 (10.0)	Quality of life	Self	36	7-point responses	Last two weeks	Multiple ^c
IBDQ-32	Inflammatory Bowel Disease Questionnaire ¹⁷	36 (60.6)	Quality of life	Self, Interviewer	32	7-point Likert scale	Last two weeks	Multiple ^d
IBDQ-9	Inflammatory Bowel Disease Questionnaire – short form ^{28,29}	1 (2.2)	Quality of life	Self, Interviewer	9		Last two weeks	English
IBDSI	Inflammatory Bowel Disease Stress Index ¹⁹	2 (4.3)	Overall life satisfaction, body image, relationships, school, recreation, sexuality, psychosomatic symptomatology	Self, Interviewer	8	0 (no impact) – 3 (great deal of impact)	Today	English
RFIPC	Rating Form of IBD Patient Concerns ¹⁸	5 (10.9)	Worries and concerns associated with IBD and its treatment	Self	25	Visual Analog Scale	Today	Multiple ^e
SIBDQ	Short Inflammatory Bowel Disease Questionnaire ³⁰	5 (10.9)	Quality of life	Self, Interviewer	10	7-point Likert scale	Last two weeks	Multiple ^f
WPAI:CD	Work Productivity and Activity Impairment: Crohn's Disease ³¹	1 (2.2)	Work and activity impairment	Self, Interviewer, Telephone	6	Rating 0-10, Number of hours	Last seven days	Multiple ^g

a Percentage of studies in which IBD-specific PROMs were applied; more than one PROMs could be applied in one study.

b At least one year after surgery.

c Original language: English; translated to Danish, Dutch, Finnish, French, German, Hebrew, Italian, Norwegian, Slovak, Spanish, Swedish.

d Original language: English; translated to Arabic, Bengali, Bulgarian, Chinese, Czech, Danish, Dutch, Finnish, French, German, Greek, Gujarati, Hebrew, Hungarian, Italian, Japanese, Latvian, Lithuanian, Malayalam, Marathi, Norwegian, Polish, Portuguese, Punjabi, Romanian, Russian, Serbian, Sesotho, Slovakian, Spanish, Swedish, Tamil, Telugu, Ukrainian, Urdu for India, Xhosa, Zulu.

e Original language: English; translated to French, German, Hebrew, Italian, Portuguese, Spanish, Swedish.

f Original language: English; translated to Arabic, Bengali, Bulgarian, Chinese, Czech, Danish, Dutch, Finnish, French, German, Greek, Gujarati, Hebrew, Hungarian, Italian, Japanese, Latvian, Lithuanian, Malayalam, Marathi, Norwegian, Polish, Portuguese, Punjabi, Romanian, Russian, Serbian, Sesotho, Slovakian, Spanish, Swedish, Tamil, Telugu, Ukrainian, Urdu for India, Xhosa, Zulu.

g Original language: English; translated to Czech, Danish, Dutch, Finnish, French, German, Greek, Hungarian, Icelandic, Italian, Japanese, Norwegian, Polish, Portuguese, Slovak, Slovene, Spanish, Swedish.

4.3 Linkage of the identified PROMs

In total, the eight IBD-specific PROMs included 129 items. Ninety of them (69.8%) were linked to 45 specific ICF categories: 23 *Body Functions*' categories (51.1%), 1 *Body Structures*' category (2.2%), 13 categories of the component *Activities and Participation* (28.9%) and 8 *Environmental Factors*' categories (17.8%). Twenty-eight items (21.7%) were linked to *Personal Factors* (pf) and 11 items to 'nd' and 'nc' (8.5%), respectively.

The Kappa statistic for the linking of the items was 0.61 [95% CI: 0.53 – 0.66].

4.4 Content comparison of the identified PROMs

In detail, the IBDQ-32 covers the highest (n=24) and the CGQL the lowest number of ICF categories (n=1). The most *Body Functions*' categories were found in the IBDQ-32 (n=14) followed by the IBDQOL (n=12). The following PROMs address the most categories of the component *Activities and Participation*: IBDQOL (n=7), IBDQ-32 (n=6) and IBDSI (n=6).

Tables 3 to 5 show the coverage of ICF categories from the components *Body Functions*, *Body Structures*, *Activities and Participation* and *Environmental Factors* by the identified PROMs. None of the linked ICF categories are contained in all PROMs. The most frequently identified categories are 'b1300 Energy level', 'b5254 Flatulence' (IBDQOL, IBDQ-32, IBDQ-9, RFIPC and SIBDQ) and 'd920 Recreation and leisure' (IBDQOL, IBDQ-32, IBDSI, IBS-QOL and SIBDQ).

Table 3 ICF categories of the components *Body Functions* and *Body Structures* addressed in IBD-specific PROMs

ICF categories		PROMs							
ICF code	ICF title	CGQL	IBDQOL	IBDSI	IBDQ-32	IBDQ-9	RFIPC	SIBDQ	WPAI:CD
b	Body functions								
b1	Mental functions								
b130	Energy and drive functions	+				+			
b1300	Energy level		+		+	+	+	+	
b1302	Appetite		+						
b1308	Energy and drive functions, other specified				+	+			
b1341	Onset of sleep		+						
b1342	Maintenance of sleep		+		+				
b1343	Quality of sleep				+				
b152	Emotional functions		+		+				+
b1801	Body image			+					
b2	Sensory functions and pain								
b280	Sensation of pain						+		
b2801	Pain in body part				+				+
b28012	Pain in stomach or abdomen				+				+
b5	Functions of the digestive, metabolic and endocrine systems								
b5150	Transport of food through stomach and intestines		+		+	+			
b525	Defecation functions		+		+		+		+

Table 3 continued

ICF categories		PROMs							
ICF code	ICF title	CGQL	IBDQOL	IBDSI	IBDQ-32	IBDQ-9	RFIPC	SIBDQ	WPAI:CD
b5253	Faecal continence		+						
b5254	Flatulence		+		+	+	+	+	
b530	Weight maintenance functions		+		+			+	
b535	Sensations associated with the digestive system				+	+			
b5350	Sensation of nausea					+			
b5351	Feeling bloated		+		+				
b5352	Sensation of abdominal cramp		+		+	+			
b6	Genitourinary and reproductive functions								
b640	Sexual functions						+		
b660	Procreation functions						+		
s	Body structures								
s5	Structures related to the digestive, metabolic and endocrine systems								
s540	Structures of intestine			+		+			

CGQL Cleveland Global Quality of Life (Faszio Score); IBDQOL Inflammatory Bowel Disease Quality of Life Questionnaire; IBDSI IBD Stress Index; IBDQ-32 Inflammatory Bowel Disease Questionnaire; IBDQ-9 Inflammatory Bowel Disease Questionnaire short form; RFIPC Rating Form of IBD Patient Concerns; SIBDQ Short Inflammatory Bowel Disease Questionnaire; WPAI:CD Work Productivity and Activity Impairment: Crohn's Disease.

Table 4 ICF categories of the component *Activities and Participation* addressed in IBD-specific PROMs

ICF categories		PROMs									
ICF code	ICF title	CGQL	IBDQOL	IBDSI	IBDQ-32	IBDQ-9	RFIPC	SIBDQ	WPAI:CD		
d	Activities and Participation				+						
d2	General tasks and demands										
d230	Carrying out daily routine										+
d7	Interpersonal interactions and relationships			+							
d760	Family relationships		+								
d770	Intimate relationships			+			+				
d7702	Sexual relationships		+		+						
d8	Major life areas										
d820	School education		+	+	+						
d850	Remunerative employment		+		+						+
d859	Work and employment, other specified and unspecified			+							
d9	Community, social and civic life					+					
d910	Community life		+	+	+			+			
d920	Recreation and leisure		+	+	+			+			
d9201	Sports		+		+			+			

CGQL Cleveland Global Quality of Life (Faszio Score); IBDQOL Inflammatory Bowel Disease Quality of Life Questionnaire; IBDSI IBD Stress Index; IBDQ-32 Inflammatory Bowel Disease Questionnaire; IBDQ-9 Inflammatory Bowel Disease Questionnaire short form; RFIPC Rating Form of IBD Patient Concerns; SIBDQ Short Inflammatory Bowel Disease Questionnaire; WPAI:CD Work Productivity and Activity Impairment: Crohn's Disease.

Table 5 ICF categories of the component *Environmental Factors* addressed in IBD-specific PROMs

ICF categories		PROMs							
ICF code	ICF title	CGQL	IBDQOL	IBDSI	IBDQ-32	IBDQ-9	RFIPC	SIBDQ	WPAI:CD
e	Environmental factors				+				
e1	Products and technology								
e1101	Drugs		+				+		
e1151	Assistive products and technology for personal use in daily living						+		
e1501	Design, construction and building products and technology for gaining access to facilities inside buildings for public use		+		+				
e165	Assets						+		
e4	Attitudes				+				
e5	Services, Systems and policies								
e580	Health services, systems and policies						+		
e5800	Health services						+		

CGQL Cleveland Global Quality of Life (Faszio Score); IBDQOL Inflammatory Bowel Disease Quality of Life Questionnaire; IBDSI IBD Stress Index; IBDQ-32 Inflammatory Bowel Disease Questionnaire; IBDQ-9 Inflammatory Bowel Disease Questionnaire short form; RFIPC Rating Form of IBD Patient Concerns; SIBDQ Short Inflammatory Bowel Disease Questionnaire; WPAI:CD Work Productivity and Activity Impairment: Crohn's Disease.

Table 6 Other aspects addressed in IBD-specific PROMs

Other aspects		PROMs							
Coding	Title	CGQL	IBDQOL	IBDSI	IBDQ-32	IBDQ-9	RFIPC	SIBDQ	WPAI:CD
pf	Personal factors		+	+	+	+	+	+	
nd	Not definable			+			+		
nd-hc	Not definable: Health condition						+		
nd-gh	Not definable: General health	+	+		+	+			
nd-QoL	Not definable: Overall quality of life	+							
nc	Not covered						+		

5. Discussion

This doctoral thesis provides an overview and comparison of IBD-specific PROMs with respect to their contents covered using the ICF as a reference. The examination of the PROMs' contents covered on the smallest possible units, namely, the items of the questionnaires. This offers a clear and precise picture of the addressed PROMs contents identified in this study and enables direct comparisons to be made. The results of the content comparison provide valuable information to facilitate and account for the selection of appropriate IBD-specific PROMs for different purposes of data collection in clinical and research settings.

Clinicians and researchers who define the aspects they want to measure in terms of the ICF can directly use Tables 3 to 5 to look up which of the examined PROMs cover those aspects. For example, a researcher dealing with the question how IBD affects the sleep function of persons with IBD will find the ICF category 'b1342 Maintenance of sleep' in Table 3. In this table the researcher can see that the items of the IBDQOL and the IBDQ-32 address this area of functioning and might, therefore, present an adequate choice in this context. Thus, PROMs and their items can be easily matched to each other by using the ICF, thereby simplifying the selection of PROMs.

Overall, the areas of functioning addressed in the items of the identified PROMs are very diverse. There are just 4 ICF categories out of the 45 ICF categories linked to the 90 PROMs items that are addressed in at least 4 out of 8 PROMs. This indicates that the individual PROMs and their items differ widely in content. Examination of the PROMs' contents remarkably shows that a high percentage of the linked ICF categories applies to only two of the eight selected PROMs, namely IBDQOL and IBDQ-32. This means that many topics are addressed in these two PROMs, and no other PROMs include them.

An important finding of this study refers to the representation of pain in IBD. Only three PROMs (IBDQ-32, RFIPC, SIBDQ) include items addressing sensory functions and pain, even if in clinical practice pain is stated in the case history of many persons diagnosed with IBD.^{41,42} Bielefeldt and colleagues show that not only inflammation,

but also bowel obstructions, can manifest as pain, and even a subgroup of IBD patients without evidence of overt inflammation, obstruction or other clinically defined abnormalities continue to have pain. Thus, pain or fear of pain constitute a significant burden for persons with IBD and can reduce their quality of life.^{43,44}

One of the most frequently covered ICF categories is 'b1300 Energy level'. Rooy and colleagues point out that the level of energy is the most intense concern of persons with IBD if the RFIPC is used as a PROM for examination.⁴²

In three PROMs 'b152 Emotional functions', which includes feelings like sadness, happiness, anxiety or sorrow, is covered (IBDQOL, IBDQ-32, SIBDQ). Whereas 'b1801 body image' which includes the feeling of being too fat or too thin is represented in only one PROM (IBDSI). Muller and colleagues show that the majority of persons with IBD report that the disease affects their body image; particularly females who have had abdominal surgery describe a negative impact on their body image.⁴⁵

The question about maintenance of sleep or the quality of sleep is addressed in only two PROMs. Considering the fact persons with IBD complained of repeated awakening at night twice as often as healthy controls⁴⁶ this area of functioning is poorly represented in the identified PROMs. A healthy sleep-wake cycle is critical for the regulation of immune and neuroendocrine functions⁴⁷, and sleepiness and fatigue are often the cardinal manifestations of acute inflammatory disorders⁴⁴. For persons with IBD, repeated awakenings are, among other reasons, attributed to the need to use the bathroom. A further important finding of this study is that none of the identified PROMs and their items covered the category 'd530 Toileting' which refers to coordinating and managing defecation and getting to an appropriate place for defecation. Stjernman and colleagues show that persons with IBD are often concerned about their loss of bowel control and are worried about finding a toilet in time.⁴⁸

It is interesting that only 13 categories of the component *Activities and Participation* were linked to the items of the IBD-specific PROMs. In a qualitative study Peyrin-Biroulet and colleagues show that various aspects of activities and participation (e.g., sexual relationships, managing diet and fitness, remunerative employment) are important from the patient perspective.⁴⁹ These areas are poorly represented in IBD-specific PROMs. However, some of the identified PROMs and their items (IBDQOL, IBDQ-32, IBDSI) cover a few ICF categories addressing activities of daily living and social participation: interpersonal interactions, work or school education or community, social and civic life.

It could be argued that the results of this investigation suggest that the lack of coverage of important areas by the IBD-specific PROMs could be compensated by the joint use of IBD-specific and generic PROMs, such as the 36-Item Short Form Survey (SF-36).⁵⁰ However, a comparison of the results of this study with the results of a previous one, in which the similarities and differences in content of the most widely used generic PROMs were studied, shows that these PROMs are very heterogeneous and that, as is the case in the condition-specific PROMs, they frequently do not cover some important areas in IBD, such as toileting and sexuality⁵¹. Toileting is only covered in the Spitzer's Quality of Life Index (QL-I)⁵² and intimate relationships and sexuality only in the WHO Quality of Life-BREF (WHOQOL-BREF)⁵³, World Health Organization Disability Assessment Schedule II (WHODAS II)⁵⁴ and Nottingham Health Profile (NHP)⁵⁵. The generic PROMs analysed in the mentioned study show a very high level of depth of coverage and granularity in mobility, which is a less relevant area in IBD. This comparison suggests that when selecting instruments for an investigation a very careful study of the contents of both the IBD-specific and generic PROMs is necessary to ensure that all relevant aspects of IBD and all study endpoints are covered without imposing unnecessary burden on the patients. The study of the psychometric properties is also important. For example, McColl et al. recommend the use of both types of PROMs in parallel based on the comparison of the discriminatory power of the SF-36 and the IBDQ.⁵⁶ While disease activity was more highly correlated with IBDQ scores than with SF-36 scores, significant differences with respect to disease severity were found in the SF-36's energy/fatigue and social-function scales.

Last but not least, an ICF-based examination of the PROMs' contents could facilitate the development of new or modified PROMs. Presenting an overview of the most- or least-frequently mentioned ICF categories covering the items of the identified PROMs this paper could be used to identify areas of functioning and health. This information could lead to the development of more specific PROMs for clinical evaluation and research in IBD.

The study has several limitations that have to be mentioned. The systematic literature review used to identify IBD-specific PROMs was based on a simplified review method using specific, rather than sensitive, search strategies. For practicability reasons, the number of abstracts to be checked was decreased by a random selection. Moreover, we largely relied on information contained in abstracts. We did not consider other outcome measures reported in the full-text articles of the retrieved studies (e.g. disease classifications or indices). However, in comparison to other reviews on PROMs in IBD,^{18,57} the PROMs identified in this paper cover the most frequently used and established PROMs in IBD.

In this doctoral thesis the contents of IBD-specific PROMs and their items were examined to provide an overview of the areas of functioning and disability addressed by these PROMs using the ICF as a reference. This overview should facilitate the selection of PROMs in clinical practice and research. This study does not claim to be complete in terms of the frequencies of the identified PROMs. It is a first proposal to introduce a new tool, the ICF, for content comparison among IBD-specific PROMs and described its advantages by means of the given analyses. The method still can be explained without having analyzed all possibly available full-text articles. Finally, the linking process was performed by two medical doctors trained in the ICF and the application of the linking rules. However, it remains unclear whether other health professionals would have decided differently.

6. Conclusion

An overview that examines the content of IBD-specific PROMs using the ICF as a reference has not been published so far. This doctoral thesis offers a clear and precise picture of the addressed PROMs and their contents and enable physicians and researchers a direct comparison of these contents. The ICF provides a useful framework for examining and comparing IBD-specific PROMs and their items with respect to the areas of functioning and disability covered. This information can be useful in selecting PROMs for clinical practice, as well as for any kind of investigations in which functioning and disability of persons with IBD is a relevant study outcome. None of the PROMs identified in this study is ideal for all applications. However, after having decided on “what should be measured”, this study may well assist clinicians and researchers in deciding on the most suitable PROM. The results of this study emphasize the need for a comprehensive PROM covering the whole spectrum of functioning and disability in IBD.

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8. List of abbreviations

CGQL Cleveland Global Quality of Life

CENTRAL Cochrane Central Register of Controlled Trials

CINAHL Cumulative Index to Nursing and Allied Health Literature

EMBASE Excerpta Medica Database

IBDQOL Inflammatory Bowel Disease Quality of Life Questionnaire

IBDSI IBD Stress Index

IBDQ Inflammatory Bowel Disease Questionnaire

ICF International Classification of Functioning, Disability and Health

MEDLINE Medical Literature Analysis and Retrieval System Online

PROM Patient-reported outcome measure

RFIPC Rating Form of IBD Patient Concerns

SIBDQ Short Inflammatory Bowel Disease Questionnaire

WPAI:CD Work Productivity and Activity Impairment: Crohn's Disease

9. List of figures and tables

Figure 1: Structure of the International Classification of Functioning, Disability and Health

Figure 2: Structure of the International Classification of Functioning, Disability and Health; hierarchical arrangement

Figure 3: Procedure of the systematic literature review

Table 1: Countries of origin of the identified studies

Table 2: Characteristics and frequencies of the identified IBD-specific PROMs in the included studies

Table 3: ICF categories of the components Body Functions and Body Structures addressed in IBD-specific PROMs

Table 4: ICF categories of the component Activities and Participation addressed in IBD-specific PROMs

Table 5: ICF categories of the component Environmental Factors addressed in IBD-specific PROMs

Table 6: Other aspects addressed in IBD-specific PROMs

10. Appendix

Appendix 1 Eligibility criteria

Inclusion criteria	Exclusion criteria
Formal criteria	
<u>Publication type:</u> Journal article (original paper)	Review (Topic Overview) or Meta-Analyses Comment Letter Editorial Guideline Conference Report Book chapter Dissertation
<u>Language:</u> English	Other than English
<u>Year of publication:</u> 1999-2009	Other than 1999-2009
<u>Multiple publications:</u> Journal with the highest impact factor in the case of multiple publications; the most recent publication will be considered	Journal with lower than the highest impact factor in the case of multiple publications; the less recent publications will be excluded
Study design	
<ul style="list-style-type: none"> • Randomized controlled trial or randomized clinical trial (RCT) • Clinical controlled trial (CCT) • Cross-sectional study • Longitudinal observational study • Qualitative study • Psychometric study • Diagnostic efficacy evaluation • Register study • Chart review 	<ul style="list-style-type: none"> • Review or Meta-Analysis • Case report/ Case series • Primary prevention study • Clinical trials phase-I /-II study • Ecologic study • Economic evaluation study or decision analysis (costs, cost/benefit, cost/ effectiveness, cost/utility, modeling, simulation) based on review or meta-analyses • Study protocol
Study population	
Human	Non-human population (animal study/ cadaver study/ genetic study/ exclusively laboratory-parameters/ in-vitro study)
Patients at age ≥ 18 yrs	Patients at age <18 yrs
<u>Sample size:</u> $N \geq 11$	Sample Size: $N \leq 10$
<u>Diagnosis:</u> Patients with inflammatory bowel diseases; main diagnosis according to ICD-10 <i>at the beginning of data collection:</i> K50 Crohn's disease [regional enteritis] .0 Crohn's disease of small intestine .1 Crohn's disease of large intestine .8 Other Crohn's disease .9 Crohn's disease, unspecified K51 Ulcerative colitis .0 Ulcerative (chronic) enterocolitis .1 Ulcerative (chronic) ileocolitis	Patients with inflammatory bowel diseases; main diagnosis according to ICD-10 K51.4 Pseudopolyposis of colon K51.5 Mucosal proctocolitis
	Patients included in the sample with main disease conditions any other than target condition at study beginning, i.e. mixed patient population (e.g. population consists of patients with diabetes or healthy controls)

Appendix 2 Example of a linked PROM

Name of PROM	Item Nr.	Item as appeared in the questionnaire	Linking first health professional		Linking second health professional		Linking final version	
			Linking unit	ICF code	Linking unit	ICF code	Linking unit	ICF code
IBDQ-9	1	How frequent have your bowel movements been during the last 2 weeks?	Frequency of bowel movements	b5158	Frequency of bowel movements	b539	Frequency of bowel movements	b5150
IBDQ-9	2	How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks?	- Feeling of fatigue - Feeling tired and worn out	b1308 b130	Frequency of being tired	b1308	- Feeling of fatigue - Feeling tired and worn out	b1308 b130
IBDQ-9	3	How much energy have you had during the last 2 weeks?	Energy	b1300	Energy level for the last 2 week	b1300	Energy level for the last 2 week	b1300
IBDQ-9	4	How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem?	Delay or cancel a social engagement because of bowel problem	d9108	Cancelling a social engagement	nd	Cancelling a social engagement	d9
IBDQ-9	5	How often during the last 2 weeks have you been troubled by cramps in your abdomen?	Trouble by cramps in abdomen	b5352	Abdominal cramp	b5352	Abdominal cramp	b5352
IBDQ-9	6	How often during the last 2 weeks have you felt generally unwell?	Feeling generally unwell	gh	Well-being	pf	Well being	gh
IBDQ-9	7	Overall, in the last 2 weeks, how much of a problem have you had with passing a large amount of gas?	Large amount of gas	b5254	Passing gas	b5254	Passing gas	b5254
IBDQ-9	8	How much of the time during the last 2 weeks have you been troubled by feeling nauseated or sick with your stomach?	- Feeling of nausea - Feeling of sick with stomach	b5350 b535	Nausea	b5350	- Feeling of sick with stomach - Nausea	b535 b5350
IBDQ-9	9	How satisfied, happy, or pleased have you been with your personal life during the last 2 weeks?	Satisfaction with personal life Happieness with personal life	pf d	General well-being	pf	Satisfaction with personal life	pf

Appendix 3 List of references of included studies

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