

# The Danish National Registry for Biological Therapy in Inflammatory Bowel Disease

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**Aim:** The aims of The Danish National Registry for Biological Therapy in Inflammatory Bowel Disease are to ensure that biological therapy and the clinical management of patients with inflammatory bowel disease (IBD) receiving biological treatment are in accordance with the national clinical guidelines and, second, the database allows register-based clinical epidemiological research.

**Study population:** The study population comprises all Danish patients with IBD (both children and adults) with ulcerative colitis, Crohn's disease, and IBD unclassified who receive biological therapy. Patients will be enrolled consecutively when biological treatment is initiated.

**Main variables:** The variables in the database are: diagnosis, time of diagnosis, disease manifestation, indication for biological therapy, previous biological and nonbiological therapy, date of visit, clinical indices, physician's global assessment, pregnancy and breastfeeding (women), height (children), weight, dosage (current biological agent), adverse events, surgery, endoscopic procedures, and radiology.

**Descriptive data:** Eleven clinical indicators have been selected to monitor the quality of biological treatment. For each indicator, a standard has been defined based on the available evidence. National results will be published in an annual report and local results on a quarterly basis. The indicators will be reported as department-specific proportions with 95% confidence intervals, and the national average will be provided for comparison. An estimated 1,200–1,300 new biological therapies are initiated each year in Danish patients with IBD.

**Conclusion:** The database will be available for research during 2016. Data will be made available by The Danish Clinical Registries ([www.rkkp.dk](http://www.rkkp.dk)).

**Keywords:** inflammatory bowel disease, biological therapy, anti-TNF- $\alpha$  agents, quality indicators, database

## Background

The incidence of inflammatory bowel disease (IBD) is increasing worldwide including Denmark.<sup>1–4</sup> During the last decades, introduction of biological therapy has changed the management of ulcerative colitis (UC) and Crohn's disease (CD).<sup>5</sup> As a consequence, the medication-related expenses of IBD therapy have increased substantially.<sup>6</sup> International and national treatment guidelines support clinicians in treatment decisions and rational clinical use of biological therapy and are used by health care providers to prioritize and regulate the costs of therapy.

## Aim of The Danish National Registry for Biological Therapy in Inflammatory Bowel Disease

To ensure a rational use of biological drugs and adherence to national guidelines, The Danish National Registry for Biological Therapy in Inflammatory Bowel Disease



(BIO-IBD) has been established in 2015. First, the aim of the database is to ensure that the choice of biological therapy and the clinical management of patients with IBD receiving biological treatment are in accordance with the national clinical guidelines<sup>7</sup> and second, the database can be used for register-based clinical epidemiological research.

The database is planned to start in March 2016, and patients will be enrolled consecutively when biological treatment is initiated. Based on recent data from The Danish National Patient Registry (NPR), we estimate that 1,200–1,300 new biological therapies are initiated each year and at a given point in time 2,700–2,800 patients are treated with biological agents.

## Study population

In Denmark (population of ~5.5 million people), all citizens have free access to a tax-supported health care system, and biological therapy is only administered in public hospitals without cost to the patient.<sup>8</sup>

For all Danish hospitals, both public and private, it is mandatory by Danish law to report diagnosis and clinical procedures to NPR. The completeness of coding in NPR is very high as 99% of all hospital discharges and out-patient clinics from somatic hospitals are recorded.<sup>9</sup> Likewise the completeness of diagnoses of IBD in NPR is very good. In one study, the validity of the IBD diagnoses in NPR was

examined using the pathology system as a reference standard, confirming that 94% of the UC and CD diagnoses were included in the NPR. The overall validity of diagnoses of CD in the NPR was 97%, and for UC 90%.<sup>10</sup> Identification of patients is based on the Danish Civil Registration System (CRS). The CRS has registered all persons alive and living in Denmark since 1968, and has a very high accuracy of Danish citizens and migrations.<sup>11,12</sup>

The availability of these nationwide Danish registries makes it possible to retrieve data on almost all patients with IBD and treatment with biological agents. Hence, the study population comprises all Danish patients with IBD (both children and adults) with UC, CD, and IBD-unclassified (IBD-U) who receive biological therapy. Patients will be enrolled consecutively when biological treatment is initiated. Eligible patients with IBD are bio-naïve patients (patients never treated with biological therapy); patients previously treated with biological therapy and stopped for >3 months, and patients already on biological therapy who, due to side effects or lack of effect, switch to another biological drug.

It is mandatory for the departments prescribing biological therapy to report these data to the BIO-IBD registry.

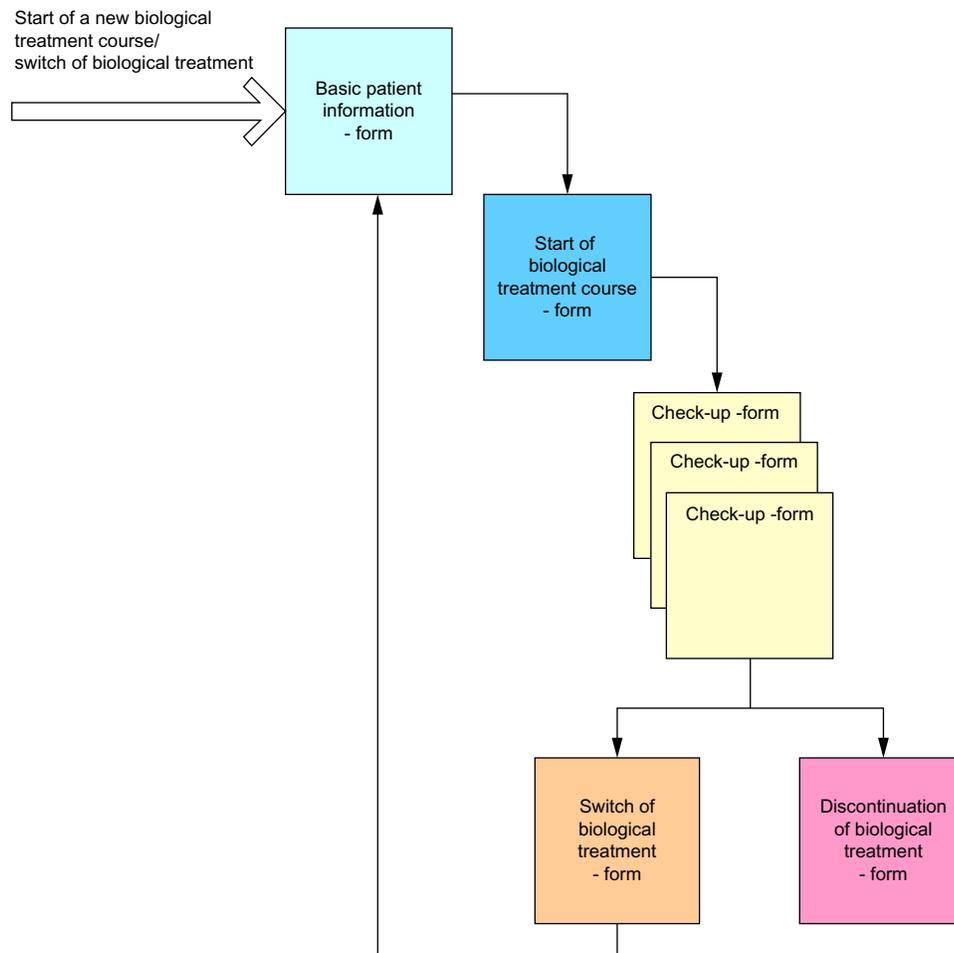
## Quality indicators

Eleven quality indicators have been defined (Table 1). Choice, background, and level of evidence for the indicators

**Table 1** Quality indicators

Quality indicator	Indicator standard (%)	Type of indicator
1CD: Percentage of patients with luminal CD for whom the indication for biological therapy is in accordance with the national guidelines	≥80	Process
2CD: Percentage of CD patients with no prior biological therapy for whom the selected first-line biological therapy is in accordance with the national guidelines	≥80	Process
3CD: Percentage of patients with CD in maintenance therapy with a biological agent, who have a minimum of two outpatient visits per year	≥80	Process
4CD: Percentage of patients in maintenance therapy with a biological agent, diagnosed with luminal CD, never having undergone surgery for CD, who have well-controlled disease (HBI score <5 or abrPCDAI <10)	≥60	Outcome
5UC: Percentage of patients with UC for whom the indication for biological therapy is in accordance with the national guidelines	≥80	Process
6UC: Percentage of UC patients with no prior biological therapy and chronic active disease for whom the selected first-line biological therapy is in accordance with the national guidelines	≥80	Process
7IBD: Percentage of UC patients with acute severe ulcerative colitis for whom the selected first-line biological therapy is in accordance with the national guidelines	≥80	Process
8UC: Percentage of patients with UC in maintenance therapy with a biological agent, who have a minimum of two outpatient visits per year	≥80	Process
9UC: Percentage of patients with UC in maintenance therapy with a biological agent, who have well-controlled disease (SCCAI <5 or PUCAI <10)	≥60	Outcome
10IBD: Percentage of patients with UC or CD, who are in steroid free remission after at least 6 months of biological therapy	≥40	Outcome
11IBD: Percentage of children with UC or CD in maintenance therapy with a biological agent, for whom data on height and weight is recorded in minimum two outpatient visits per year	≥60	Process

**Abbreviations:** abrPCDAI, Abbreviated Pediatric Crohn's Disease Activity Index; CD, Crohn's disease; HBI, Harvey-Bradshaw Index; IBD, inflammatory bowel disease; PUCAI, Pediatric Ulcerative Colitis Index; SCCAI, Simple Clinical Colitis Activity Index; UC, ulcerative colitis.



**Figure 1** Patient flow in the database.

**Notes:** Patients will be included at start or switch of biological therapy. A form for basic patient information, start of biological therapy, outpatient visit where biological therapy will be administered, switch of therapy, and discontinuation of biological therapy will be available at relevant time-point in course of therapy.

are described in The BIO-IBD Documentarist Report.<sup>13</sup> Indicators related to outcome represent clinically relevant measures, with indicator standards determined from existing literature. Indicators related to process are addressing guideline adherence and administrative issues, with indicator standards determined from consensus in the working group.

In the future, new quality indicators are to be defined and added to the registry.

## Main variables

The variables in the database are obtained by two methods: Data from NPR are used for registration of the IBD patient and basic information on diagnosis, use of biologic agent, and IBD-related procedures. This is supplemented with clinical information reported by the clinician using a national web-based input module (Supplementary materials 1, 2, and 3). This is believed to ensure the best possible data quality.

1. Data harvested from NPR: diagnosis, previous biological therapy, surgery, endoscopic procedures, radiology,

treatment dates regarding current biological therapy, and current biological agent (Table 2).

2. Data reported by the clinician include: background information (diagnosis, time of diagnosis, disease manifestation, indication for biological therapy, and previous nonbiological therapy) and contact data at outpatient visit (date of the visit, relevant clinical indices [see later], physician's global assessment, pregnancy/breastfeeding [women], height [children], weight, dosage [current biological agent], nonbiological therapy, adverse events with regard to the biological agent, and treatment decision on continuing, changing, or stopping the biological agent).
3. The clinical indices used in the database are:
  - Harvey–Bradshaw Index for CD<sup>14</sup>
  - Abbreviated Pediatric Crohn's Disease Activity Index for children with CD<sup>15</sup>
  - Simple Clinical Colitis Activity Index for UC and IBD-U<sup>16</sup>

- Pediatric Ulcerative Colitis Activity Index for children with UC and IBD-U<sup>17</sup>
- Short Health Scale.<sup>18,19</sup>

A complete list of the variables can be found in Supplementary material 2.

## Data recording

The clinician is required to ensure that every eligible patient is entered into the database upon start of biological therapy. It is recommended that data are entered in the database every time biological treatment is administered, but as a minimum twice yearly and every time changes in therapy, or side-effects occur or if therapy is stopped. In addition to this, there is a continuous data collection from the NPR, which will ensure that all eligible patients are registered, should the clinician fail to include the patient at the first visit. To ensure the completeness of the database, the departments involved in administering biological treatment will receive lists of patients with records of biological treatment codes from the NPR.

The quality of data in the database relies entirely on the clinician/IBD nurse and is the responsibility of the department giving biological treatment. It will only be possible to calculate the quality indicators if sufficient data is reported in the database. If it is not possible to calculate the indicators, the departments with incomplete data will be mentioned in the annual report. There is no official quality control but as the results are a public document and reported on a quarterly basis to the departments to regularly review their clinical performance, it is believed to motivate the clinicians to high quality in both treatment and reporting.

## Examples of research

The database will be available for research during 2016. Data will be made available by The Danish Clinical Registries (RKKP; [www.rkkp.dk](http://www.rkkp.dk)).

## Administrative issues and funding

The database is administered by a steering committee, which comprises:

- Five members of the Danish Society of Gastroenterology and Hepatology (one member from each of the five regions in Denmark)
- A pediatric gastroenterologist, member of the Danish Pediatric Society
- A documentarist (clinician to compose a report on the background and evidence for the indicators)

**Table 2** Codes from The Danish National Patient Registry to be included in the Danish Registry for Biological Therapy: ICD-10 diagnostic codes used to identify patients with IBD

Crohn's disease	K50.0–50.9	
Ulcerative colitis	K51.0–51.9	
IBD unclassified	K51.9, K52.9	
Specific drug coding:		ATC-coding used with procedures:
BOHJ18A1	Infliximab	L04AA12 or L04AB02
BOHJ18A3	Adalimumab	L04AA17 or L04AB04
BOHJ18A4	Golimumab	L04AB06
BOHJ18A5	Certolizumab pegol	L04AB05
BOHJ26	Natalizumab	L04AA23
BOHJ19H4	Vedolizumab	L04AA33
<b>Operation codes</b>		
KJFB00	Small bowel resection	
KJFB01	Laparoscopic small bowel resection	
KJFB20	Ileocecal resection	
KJFB21	Laparoscopic ileocecal resection	
KJFB30	Right side hemicolectomy	
KJFB31	Laparoscopic right side hemicolectomy	
KJFB33	Other resection of small bowel or colon	
KJFB34	Other laparoscopic resection of small bowel or colon	
KJFB40	Resection of transverse colon	
KJFB41	Laparoscopic resection of transverse colon	
KJFB43	Left side hemicolectomy	
KJFB44	Laparoscopic left side hemicolectomy	
KJFB46	Resection of sigmoid colon	
KJFB47	Laparoscopic resection sigmoid colon	
KJFB50	Other resection of colon	
KJFB51	Other laparoscopic resection of colon	
KJFB60	Resection of sigmoid colon with colostomy	
KJFB61	Laparoscopic resection of sigmoid colon colostomy and distal closure	
KJFB63	Other colon resection colostomy an distal closure	
KJFB64	Other laparoscopic colon resection with colostomy and distal closure	
KJFB96	Other gut resection	
KJFB97	Other laparoscopic gut resection	
KJFH00	Colectomy and ileorectal stoma	
KJFH10	Colectomy and ileostomy	
KJFH11	Laparoscopic colectomy and ileostomy	
KJFH20	Proctocolectomy and ileostomy	
KJFH96	Other colectomy	
KJGB00	Resection of rectum	
KJGB01	Laparoscopic resection of rectum with colorectal or coloanal anastomosis	
KJGB10	Resection of rectum with colostomy	
KJGB11	Laparoscopic resection of rectum with colostomy	
KJGB30	Abdominoperianal resection of rectum	
KJGB31	Laparoscopic and perianal excision of rectum	
<b>MRI</b>		
UXMD	MRI of abdomen and pelvis	
UXMD10	MRI of upper abdomen	
UXMD15	MRI of lower abdomen, including pelvis	
UXMD20	MRI of retroperitoneum	

(Continued)

**Table 2** (Continued)

UXMD22	MRI of abdominal wall
UXMD25	MRI of gastrointestinal tract
UXMD25A	MRI of small bowel
UXMD25B	MRI of colon
<b>CT scan</b>	
UXCD	CT scan of abdomen and pelvis
UXCD00	CT scan of abdomen
UXCD10	CT scan of upper abdomen
UXCD15	CT scan of lower abdomen, including pelvis
<b>Endoscopy</b>	
KUJ	Endoscopy of gastrointestinal tract
KUJC	Esophageal endoscopy
KUJC02	Esophageal endoscopy
KUJC05	Esophageal endoscopy with biopsy
KUJC12	Flexible esophageal endoscopy
KUJC15	Flexible esophageal endoscopy with biopsy
KUJF32	Colonoscopy
KUJF35	Colonoscopy with biopsy
KUJF42	Sigmoidoscopy
KUJF45	Sigmoidoscopy with biopsy
KUJF12	Enteroscopy through stoma
KUJF15	Enteroscopy through stoma with biopsy
KUJF92	Capsule enteroscopy
KUJF82	Double balloon endoscopy
KUJF85	Double balloon endoscopy with biopsy
<b>Chest X-ray</b>	
UXRC00	X-ray of chest
UXRC05	X-ray of chest
<b>Abdominal X-ray</b>	
UXRD	Abdominal X-ray
UXRD15	Small bowel follow-through
UXRD20	Small bowel follow-through with contrast in tube
UXRD35	Pouchografi
UXZI6	Fistulography

**Notes:** Treatment codes used to identify eligible patients with IBD. Codes used for surgery, radiology, and endoscopic procedures.

**Abbreviations:** ATC, anatomical therapeutical chemical classification; CT, computed tomography; IBD, inflammatory bowel disease; ICD, The International Classification of Diseases; MRI, magnetic resonance imaging.

- A RKKP-team (Danish Clinical Quality Databases represented by the Centre of Competence for Nationwide Clinical Registries) assigning a contact person, a data manager, an epidemiologist, and a statistician.

The members are appointed for a period of 4 years by the board of the respective societies. There is an option for one re-election.

The steering committee has no financial means of its own, but the Danish Regions' funding for clinical quality registries has secured a grant for the establishment of the database.

The BIO-IBD database operates under the Danish law on data protection, with license granted by the Danish Data Protection Agency and the Danish National Board of Health. Further individual patient consent or Ethical Review Board

approval is not required according to Danish law when data are used to monitor, secure, and improve clinical quality.

## Conclusion

Based on the indicators defined, an annual report will state the quality of biological therapy in patients with IBD treated in Denmark, both at a national and department level together with a complete overview of the data available.

In addition, results are reported on a quarterly basis to the departments to regularly review their clinical performance. The indicators will be reported as department-specific proportions with 95% confidence intervals, and the national average will be provided for comparison. For each indicator, a standard has been developed based on the available evidence.

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## Disclosure

The authors report no conflicts of interest in this work.

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