IBDREAM: registry for future-proof IBD care

Update on a nationwide IBD cohort: report June 2018

IBDREAM committee members and participating hospitals

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Contents

1. Background

In the Netherlands approximately 90000 patients suffer from inflammatory bowel disease (IBD) and its incidence appears to be rising. The disease typically manifests in the 2nd or 3rd decade of life with a remarkable impact on health-related quality of life. Although the pathogenesis of IBD is still unclear, it is hypothesized that chronic inflammation originates from an overly aggressive mucosal immune response against luminal bacteria in genetically susceptible subjects. Patients may show symptoms of diarrhea or rectal blood loss, abdominal pain, vomiting and occasionally weight loss or anemia. In combination with elevated inflammatory parameters and colonoscopy combined with histology the diagnosis can be made. Extra-intestinal manifestations such as arthritis, skin disorders and uveitis are common. The disease can lead to several complications like fistulae, abcesses and even colorectal cancer. IBD is a chronic disabling disease, frequently leading to hospitalizations, lower quality of life and work disability.

The Dutch IBD patient organization (Crohn en Colitis Vereniging Nederland, CCUVN) has shown that there is a need for personalized medical care and aims at teaching IBD patients how to take the lead and how to participate and help orchestrating their personal IBD care (CCUVN working plan 2015, http://www.crohn-colitis.nl/). Furthermore, nationwide systematic data on the course, management, quality and costs of IBD therapy are scarce.

Vision IBDREAM

IBDREAM follows the philosophy and scope of the other DREAM registries, that are also successfully implemented in clinical practice (www.dreamregistry.nl). The DREAM registry for rheumatoid arthritis is one of the largest disease-specific registries in the Netherlands and has evolved to a national quality management system where benchmarking information improves quality and efficiency of care. Various cohort studies have been performed within the DREAM registry. The organization of IBDREAM resembles the structure of the DREAM registers and promises to be equally successful.

IBDREAM **aims** to be the registry for future-proof IBD care. The core pillars of IBDREAM are

- Patient empowerment
- Integrated care
- Data-driven IBD care
- Value based IBD healthcare

Patient empowerment:

IBDREAM is a registry that was specifically designed for IBD patients and will facilitate this approach through the web-based patient portal, which will provide individual feed-back on treatment, disease activity, and quality of life and long-term follow-up data on safety and efficacy of treatment. The portal also provides a means for addressing the patient's questions before consultation with their health provider, guaranteeing their own input for consultation. With IBDREAM, the patient gains more involvement in their own disease, improving the patient empowerment.

Integrated care:

IBDREAM's Transparency in Healthcare (TiH) Online Monitoring Application (OMA) and database are fully compatible with other health applications and devices. This allows future linkage with systems used in both primary- and secondary medical care. This is crucial for a future universal 'personal health environment' (Dutch: persoonlijke gezondheidsomgeving) where patients can gain access to their complete medical file. Integration of electronical patient files of both primary and secondary care, will lead to a lower registration burden of clinicians and more involvement of the patient.

Data-driven IBD care

The goal is to improve the quality of care for IBD patients in the Netherlands. Through IBDREAM, information will be prospectively gathered regarding diagnosis and specific IBD manifestations, clinical, laboratory and PROMs (disease activity, complications of disease, quality of life, work). Results can be used to learn as a clinician, as gastroenterology department and for benchmarking with other hospitals. Furthermore, data collection will lead to transparency of IBD care, to establishment of the real-life effectiveness and safety of

biological therapies and will eventually lead to optimization of IBD pharmacotherapy.

Value-based IBD care

With all new promising but expensive treatment options the main proportion of healthcare costs shifted from in-hospital care to medication costs. With the rising healthcare costs, value based healthcare is becoming more important, and is becoming essential for making responsible decisions by decision makers and clinical management. The patient-value (health-outcomes / costs) is the main focus. The IBDREAM registry is the pre-eminent tool to determine Patient Value, as it collects longitudinal data as it follows the whole patient journey. Both direct and indirect costs can be obtained from all data collected. Furthermore, more insight in the short-term and long-term effectivity of different treatment strategies can be established. By learning from and reacting to these outcomes, a more effective and cost-effective IBD care can be contrived in the future.

$$\text{Patient Value} = \frac{\text{Health Outcomes}}{\text{Cost}}$$

Contents of year report

This document reports the two-year follow-up data of a nationwide IBD cohort in the Netherlands. The following research questions will be addressed in this report.

1. What is the number of patients included in total?
2. What are the baseline characteristics of enrolled patients?
3. How many patients used IBDREAM for questionnaires?
4. What was the most recent reported disease activity?
5. How many patients were treated with biologic agents?
6. How many adverse events were reported?

2. Methods IBDREAM

2.1 General information IBDREAM

In 2016, IBDREAM started with the prospective real-life data collection of IBD patients in five medical centers in the Netherlands: Radboud University Medical Center, Nijmegen, Medisch Spectrum Twente, Enschede, Onze Lieve Vrouwe Gasthuis, Amsterdam, Franciscus Gasthuis en Vlietland, Rotterdam, and Jeroen Bosch Ziekenhuis, Den Bosch. Last year, several other hospitals have expressed their interest in adopting IBDREAM in their day-to day care. The registry follows the patient journey and contains integrated information on diagnosis, disease activity, therapy, laboratory results, quality of life and other outcomes over time. Patients are subsequently followed during the course of their chronic disease. This will allow for collection of data on long-term efficacy and safety of medication, with special interest in biologicals. As the regular patient care is followed and no additional treatments take place, there is no burden on the patient. Data collection by the IBDREAM registry is started after informed consent. In 2018 the *Dutch Health Care Inspectorate* (Dutch: *Inspectie voor gezondheidszorg*) reviewed and approved the IBDREAM registry in Medisch Spectrum Twente, proving that the registry meets all the latest legal requirements.

2.2 Patients

The study design is a multi-center registry. In 2016, IBD patients treated with biologicals (such as infliximab, adalimumab, ustekinumab, vedolizumab and godulimumab and tofacitinib) were included, and subsequently patients with other immunosuppressive therapy like thiopurines and methotrexate were asked informed consent by their treating physician. Data collection is continued even after cessation of immunosuppressive therapy. Inclusion started in May 2016 and in 2018, only 2 years later, already over 2000 patients provided consent and were included.

2.3 Project group

The following hospitals participate in the IBDREAM project.

1. Radboud University Nijmegen Medical Centre, Nijmegen, Dr. F. Hoentjen
2. University of Twente and Medisch Spectrum Twente, Enschede, Dr. M. Russel
3. Onze Lieve Vrouwe Gasthuis, Amsterdam, Drs. J. Jansen
4. Franciscus Gasthuis en Vlietland, Rotterdam, Dr. R. West
5. Jeroen Bosch hospital, Den Bosch, Drs. T. Römkens

The committee consists of one gastroenterologist from every participating hospital. Furthermore, the daily management is in the hands of the above mentioned project managers, supported by M. de Jong (phd candidate) and dr. Harald Vonkeman (ICT management).

IBDREAM committee members:

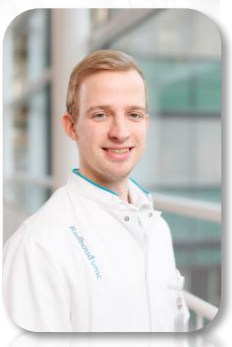
Dr. Frank Hoentjen, Gastroenterologist Radboudumc Nijmegen: Chairman of IBDREAM.

Dr. Maurice Russel, Gastroenterologist MST Enschede: Treasurer of IBDREAM.

Drs. Jeroen Jansen, Gastroenterologist OLVG Amsterdam: Secretary of IBDREAM.

Dr. Rachel West, Gastroenterologist Franciscus Gasthuis en Vlietland Rotterdam: Board member of IBDREAM.

Drs. Tessa Römkens, Gastroenterologist JBZ Den Bosch: Board member of IBDREAM.



Drs. Michiel de Jong, PhD candidate IBDREAM Radboudumc Nijmegen.

Dr. Harald Vonkeman, ICT management IBDREAM.

2.4 Facilitation

This project is supported by an unrestricted grant from:

The Netherlands Organization for Health Research & Development: **ZonMw**

And is currently facilitated by:

And facilitated in the past by:

3. Methodology IBDREAM

3.1 Inclusion criteria

1. Diagnosis of IBD (Crohn's disease, ulcerative colitis or unclassified IBD) (according to the combination of clinical, endoscopic, histologic and radiologic criteria used as a cold standard) (1).
2. Above the age of 18 years
3. Patient treated with biologic agents (both biological-experienced and naïve patients):
    - Infliximab
    - Adalimumab
    - Golimumab
    - Vedolizumab
    - Ustekinumab
    - Tofacitinib (future)
4. Patients treated with other immunosuppressive therapy:
    - Azathioprine
    - 6-Mercaptopurine
    - 6-Tioguanine
    - Methotrexate
5. Signed informed consent by the patient for the use of medical information and health-related quality of life information.

3.2 Treatment

Although dosing occurs at the discretion of the attending gastroenterologist, in general, patients start treatment according to national guidelines.

- Adalimumab: 40 mg per two weeks subcutaneous;
- Infliximab: 5 mg/kg every 8 weeks intravenous after loading doses at week 0, week 2 and week 6;
- Golimumab: 50 mg (< 80 kg) or 100 mg (> 80 kg) every 4 weeks after loading doses at week 0 and week 2;
- Vedolizumab: every eight weeks intravenous after loading doses at week 0, week 2, and

week 6 in the following dosing scheme: 300 mg.

- Ustekinumab: 6 mg/kg IV loading dose followed by 90 mg s.c. every 8-12 weeks.
- Tofacitinib: 5-10 mg oral twice daily

All start and stop dates, doses, changes in doses and reasons for changes have been registered.

3.3 Data management

3.3.1 Data collection

Login in the web-based environment is possible by both caregiver and patient. Consequently, added or updated information by the other party is accessible in real-time. Each caregiver, such as the gastroenterologist, IBD nurse and physician assistant have their own personal passwords to access the electronical system. Physicians and nurses can only access IBDREAM if their identity has been verified using their BIG registration number. Patients are provided their own passwords from their caregiver after signing informed consent.

After uploading the patient medical history, including comorbidities, prior surgery and medication, follow-up is collected prospectively. Every outpatient visit, new prescribed medication will be updated. In addition, diagnostic results, clinical outcomes (Harvey Bradshaw Index/ Short Clinical Colitis Activity Index and Physician Global Assessment), and past events (adverse events, hospitalization, surgery) are updated. To capture the patient perspective, patients are asked to fill in questionnaires twice yearly, the results are discussed during the hospital visits. These questionnaires capture quality of life, experienced disease control and

influence of disease on work and daily life (*for more details: see paragraph 3.4)*. All outcomes are presented in tables and visualized in graphs. In these graphs, different scores are shown over time, and information about the medication at time of the results is added.

The total packages of clinician- and patient reported outcomes gives a perfect overview of the patient's current and past disease. Hospital use this overview for multidisciplinary meetings.

In 2018, a large proportion of the database has been reviewed for inconsistencies and errors, showing a very high percentage of up-to date patient files. This quality control is part of a standard check for inconsistencies. Flaws and corrected if necessary. We strive to complete the data-sharing with the hospital files in the near future, to eliminate all risk of errors.

3.3.3 Privacy and security measures

Strong security measures are in place in the Transparency in Healthcare (TiH) Online Monitoring Application (OMA) and database to ensure the safety of patients records. Access to the system is only possible via log-in codes and personal passwords, which must comply with a minimum level of complexity and which must be periodically renewed.
Anonymous patient records are stored in a secured environment that adheres to all available international guidelines, including the new Dutch privacy legislation 'Algemene verordening gegevensbescherming' which is based on security guidelines established by the European Union.

3.3.3 Data extraction

Researchers who are affiliated with IBDREAM can download anonymous data to address specific research questions, only after approval by the IBDREAM regulatory board.

3.4 Detailed outcome measures

The assessments will be performed during every visit. Not only the clinician-based outcomes (laboratory results, endoscopy reports, physician assessment) are reported, we specifically aimed to capture the patient related outcomes (PROMs) as well. Disease activity is measured by

inflammatory parameters, CRP and fecal calprotectin (FC), HBI/SCCAI and endoscopic mucosal healing rate. For measurement of disease activity, FC is used. FC is a granulocyte-derived protein measured in the stool and is a non-invasive, cheap and extensively studied biomarker used in inflammatory bowel disease (IBD) and correlates with clinical and endoscopic disease activity. The Harvey Bradshaw Index (HBI) is a validated and easy-to-use disease activity index containing 5 items of which 4 items are patient-reported. The Short Clinical Colitis Activity Index (SCCAI) is the activity index used for ulcerative colitis.

We aimed to incorporate the use of PROMs in daily practice. Therefore we use validated questionnaires in order to evaluate the selected outcome measures. Several questionnaires are filled out by patients to monitor health related quality of life of IBD patients: the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), the Inflammatory Bowel Disease (IBD) control questionnaire, the Short-Form 36 (SF 36) and to assess the work productivity and activity impairment the WPAI is used. Recently, we validated the IBD-control using IBDREAM as a reliable tool to capture disease control from a patient's perspective. Data of all participating centers are collected every patient visit and monitored following the guidelines of the participating hospitals. Furthermore, information about all medication use and adverse events is collected.

Medication:

Type of medication, start date, dose and frequency, stop date, change of dose or change of medication is described. The reason for changing dose or stopping medication is registered. When the stopping reason is classified as side effect, those side effects are described in further detail.

Adverse events:

The patient report experienced adverse events using his own IBDREAM account. Every visit possible adverse events are discussed with the patient as well. The treating physician assesses the reported adverse events to be either unrelated, possibly, probably has the possibility to or very likely related to the treatment with the medication. All adverse events are categorized as minor, mild, major or life threatening.

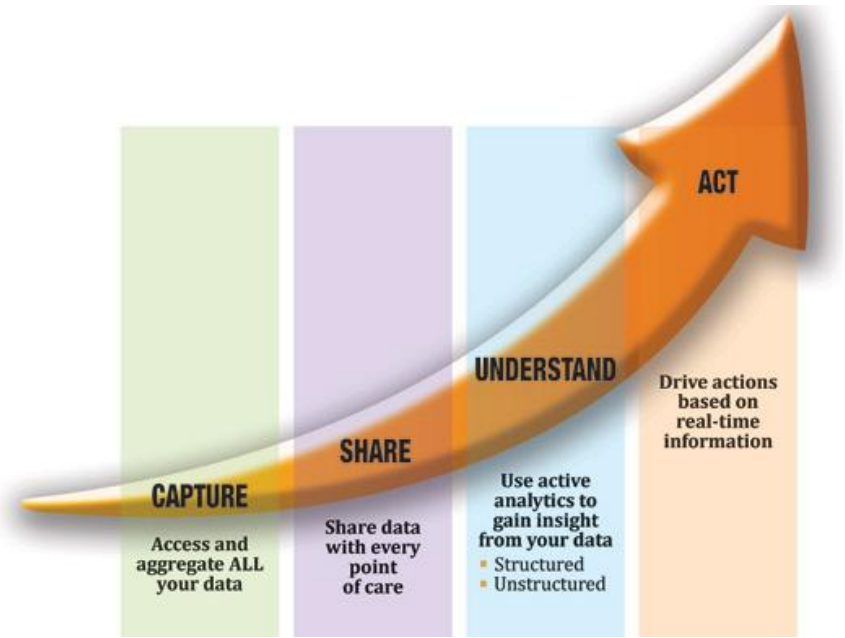
Complications and hospital admissions

4.0 IBDREAM 2.0

In collaboration with Janssen and professor Sjaak Bloem (Nyenrode University) we started the project IBDREAM2.0. The goal of this project is to further improve the user-friendliness and to exploit all possibilities of IBDREAM. Workstreams in this project include:

- the establishment of a connection between the hospital electronical patient files and IBDREAM, allowing automatic and safe data sharing. This will lead to a lower administrative burden and realize a 100% completeness of the IBDREAM database without missing values.
- Introduce Health Monitor™ : a tool developed by Professor Sjaak Bloem to assess the general health as experienced by patients. This tool can determine the personal needs of the patients, and this leads to a recommendation about the most needed intervention to improve the patient's general health. This not only includes medical treatment, but also paramedic professional aid like psychologists and dietary advisors.
- Improve the IBDREAM user-friendliness for professionals and patients.

  Minimizing the administrative burden and adding features for patients and caregivers that will further improve the added value of IBDREAM.



Results

5.1 Number of patients in the IBDREAM register

5.1.1 Inclusion

In April 2018, 1364 patients with Crohn's disease, 611 patients with ulcerative colitis, and 43 unclassified IBD were included in the IBDREAM registry. Figure 1 shows the total number of included IBD patients, 2018 patients in total by the end of April 2018. Figure 2 shows the number of patients in every participating hospital included in the registry.

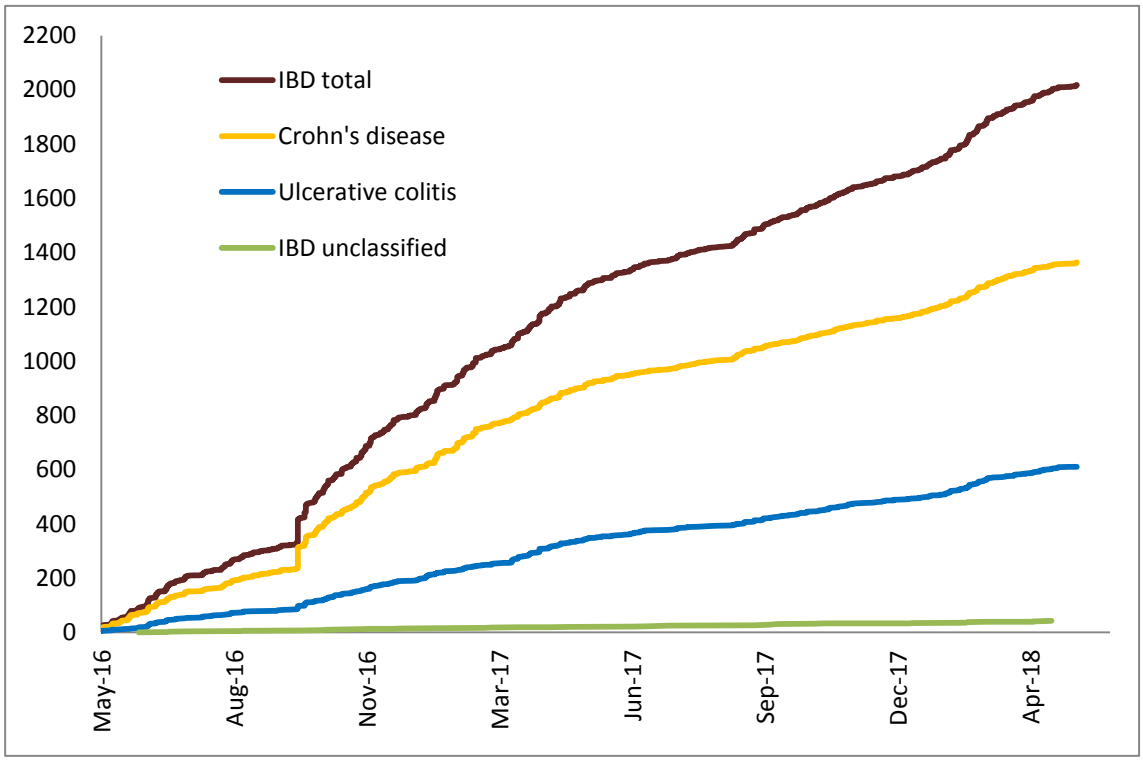


Figure 1. Included patients per IBD diagnosis

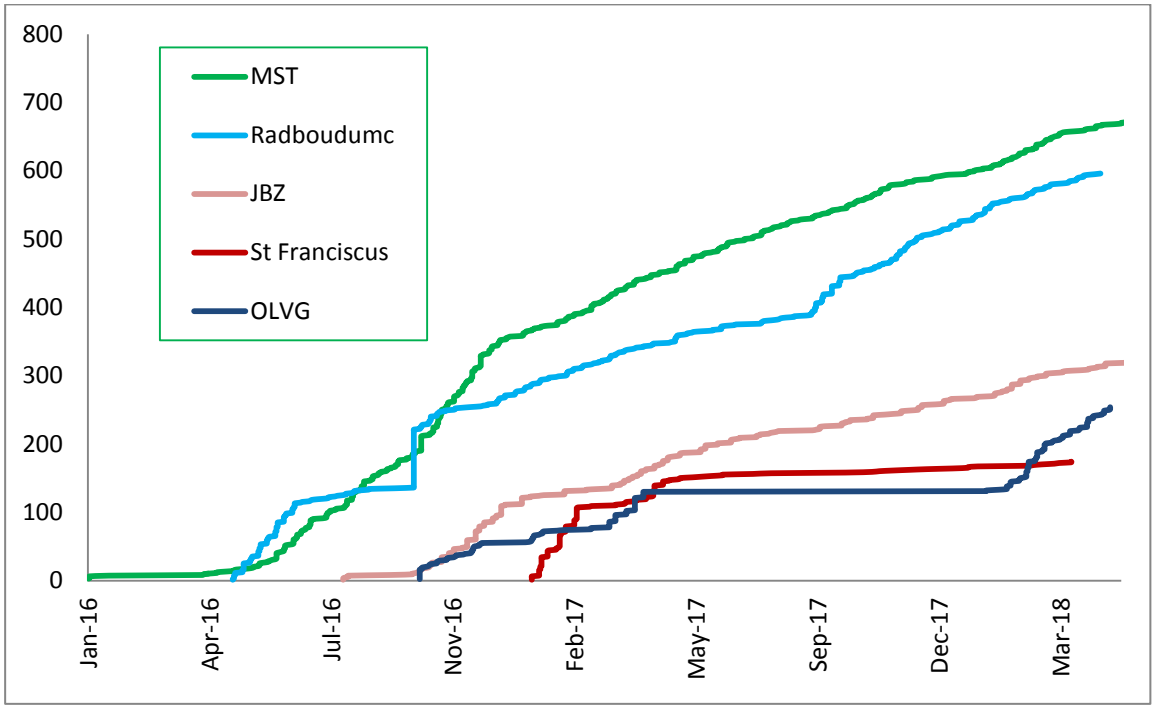


Figure 2. Included patients per hospital

5.1.2 Baseline characteristics

Table 2 shows the baseline characteristics of the 1637 enrolled patients. The majority of patients has Crohn's disease. A total of 931 patients ever started a biological and currently, 662 patients still use any biological.

Characteristic	IBDREAM
Male/female gender	874/1144
Age in April 2018, mean (+ SD)	44.4 (15.7)
Current age per decade (n)	
18-30	434
30-40	460
40-50	376
50-60	370
60-70	236
70+	142
Disease	
Ulcerative colitis, n (%)	611 (30.3)
Crohn's disease, n (%)	1364 (67.6)
Indeterminate colitis, n (%)	43 (2.1)
Current biological use, total patients	729 (100%)
Infliximab	402 (55%)
Adalimumab	184 (25%)
Ustekinumab	42 (6%)
Vedolizumab	96 (13%)
Golimumab	5 (<1%)

Table 1. Baseline characteristics

In the figure below, the distribution of patients with CD, UC, and IBD-u is shown.

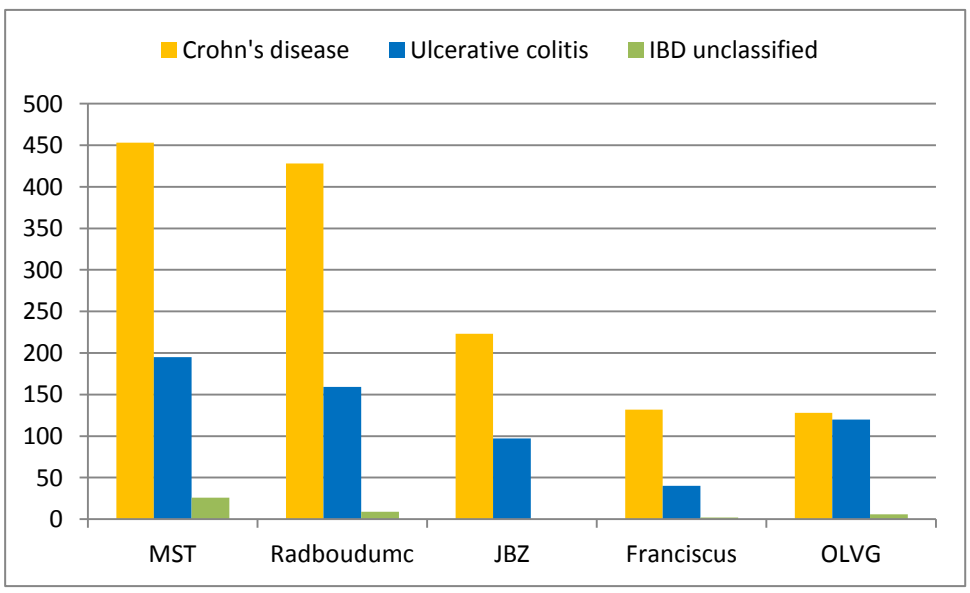


Figure 3. Distribution of IBD: Crohn's disease, ulcerative colitis and unclassified IBD.

Almost 1000 patients used IBDREAM to fill in questionnaires about quality of life (figure 4). These sets of questionnaires include the IBD-control, short-IBDQ, Short-Form 36, Work Productivity and Activity Impairment and the EuroQol5d.

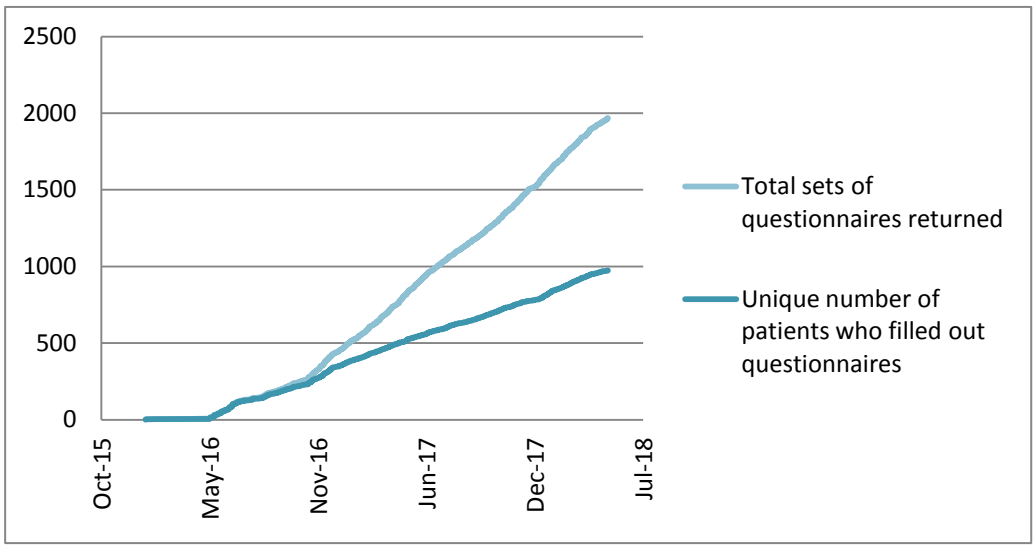


Figure 4. Total number of (patients with) patient reported outcomes measurements (PROMs) in IBDREAM

5.1.3 Clinical assessments

Overall, the majority of patients included in IBDREAM were in remission (72%) according to the most recent visit in the past year. Twenty percent of the IBD patients showed mild disease activity and 7% moderate disease activity. Only 1% of the patients were assessed as severe disease activity during their last hospital contact (figure 5). The disease activity was estimated by the physician global assessment, which is measured during every visit to outpatient clinics. The last reported HBI and SCCAI scores of all patients are reported in figure 6 and 7.

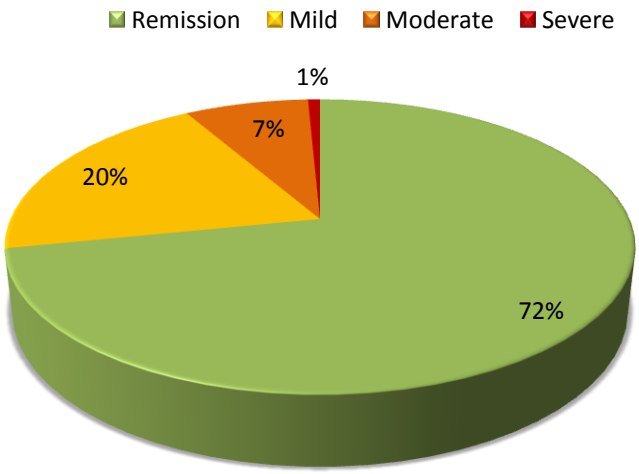


Figure 5: Disease activity of the IBDREAM IBD population in 2017 according to the physician global assessment.

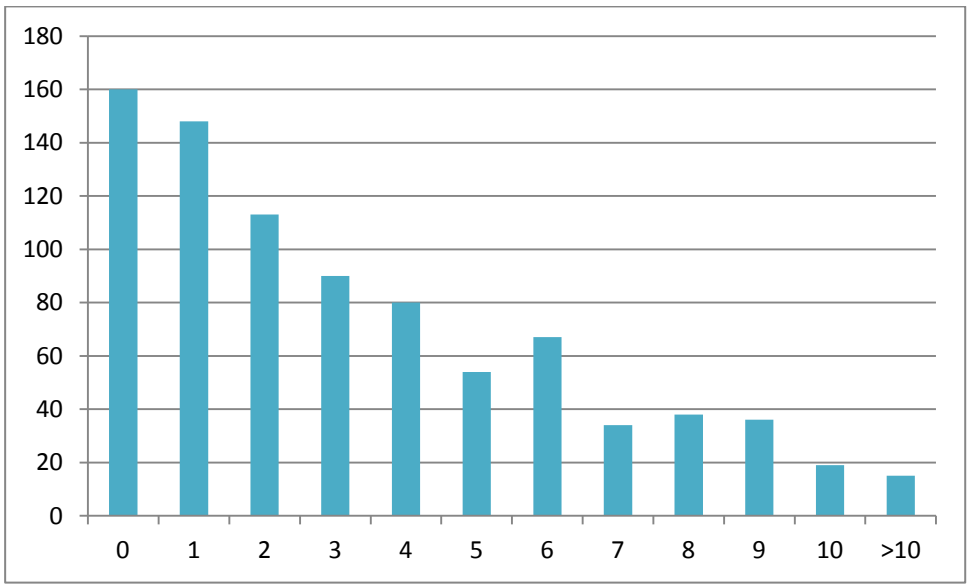


Figure 6: Number of patients with different HBI scores (total patients n=902)

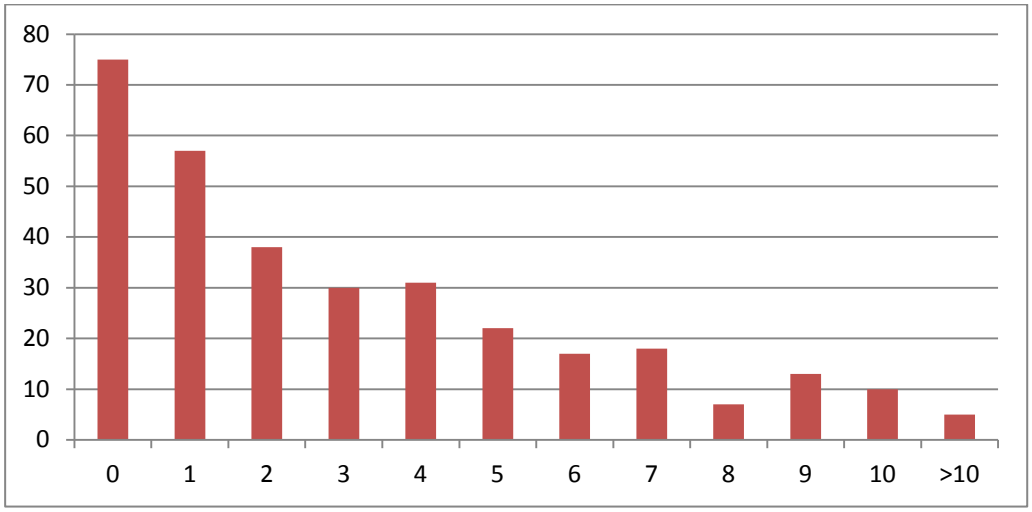


Figure 7: Number of patients with different SCCAI scores (total patients n=323)

5.1.4 Biologic agents use

In figure 8-10 the cumulative number of patients that ever started on biologicals is shown. Figure 8 includes all IBD patients, whereas fig.9 & fig.10 show only Crohn's disease and ulcerative colitis, respectively.

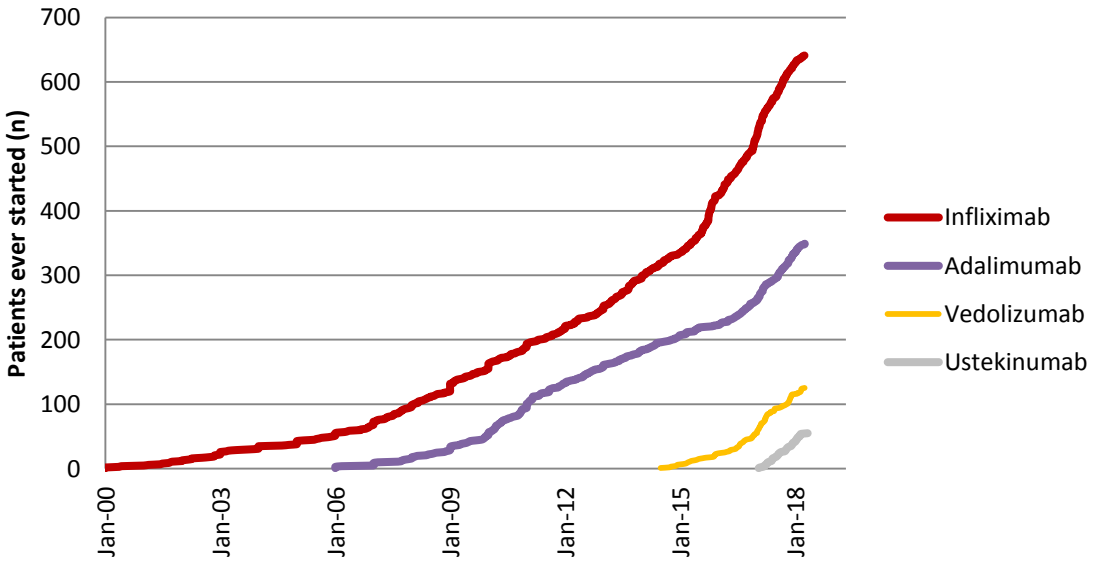


*Figure 8: Timeline showing the cumulative number of patients with **Inflammatory bowel disease** included in IBDREAM who ever started with different medication (infliximab, adalimumab, vedolizumab, ustekinumab). Patients who started multiple biologicals are included in all medication groups.*

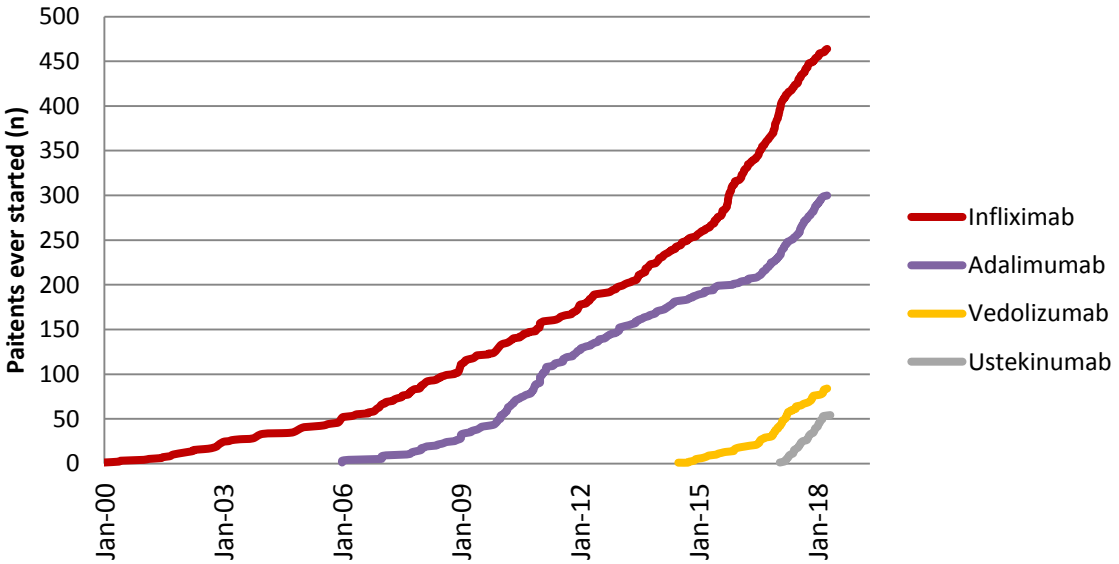


*Figure 9: Timeline showing the cumulative number of patients with **Crohn's disease** included in IBDREAM who ever started with different medication (infliximab, adalimumab, vedolizumab, ustekinumab).*

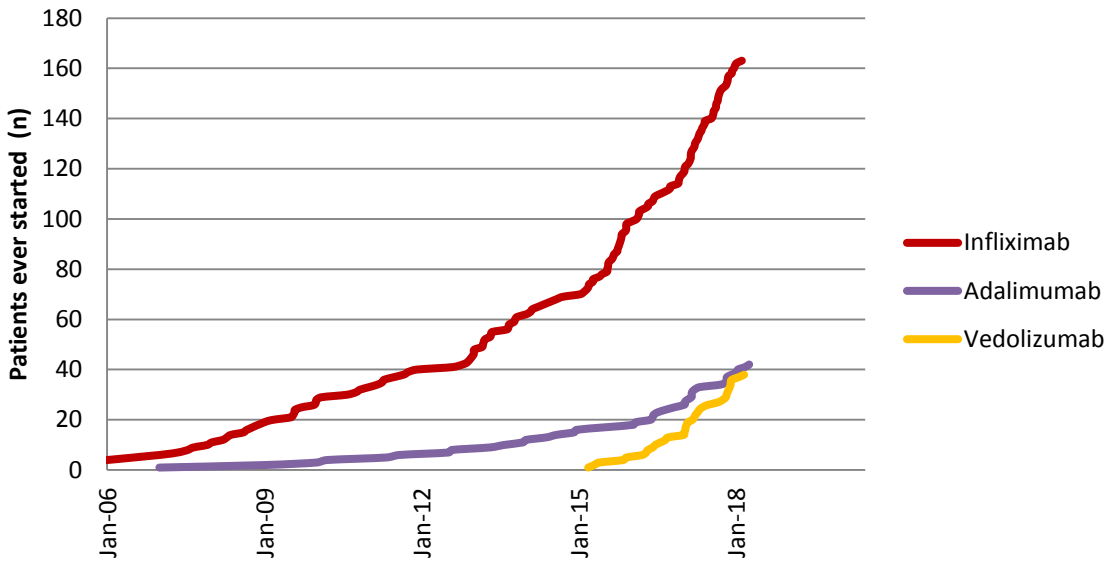


*Figure 10: Timeline showing the cumulative number of patients with **ulcerative colitis** included in IBDREAM who ever started with different medication (infliximab, adalimumab, vedolizumab).*

5.1.5 Stopping reasons biologic agents

Of the 132 patients that started adalimumab in the same year (or later) as inclusion in IBDREAM, 35 patients stopped using adalimumab. Reasons for stopping are summarized in Table 2 below.

Of the 59 patients that started ustekinumab, 9 stopped ustekinumab and 6 are still awaiting first subcutaneous injection.

Of the 117 patients that started vedolizumab in the same year (or later) as inclusion in IBDREAM, 36 patients stopped.

Stop reason	Adalimumab (n=35)	Ustekinumab (n=9)	Vedolizumab (n=36)
Ineffectivity	20	5	22
Experienced adverse events	8	3	6
Ineffectivity + experienced adverse events	3	1	1
Other	2	0	6
Remission	2	0	0
Patient died	0	0	1*

Reason of death: malignancy

Table 2. Stopping reasons for different medication.

5.1.6 Current research projects

Several research projects are already being conducted using IBDREAM. IBDREAM provides a excellenct structure to follow-up patients in a standardized manner in different hospitals. Studies include the switch study (switching infliximab to biosimilar), reducing unneeded patient visits of patients with tiopurines and the monitoring of patients on biological treatment. Furthermore, we used IBDREAM to perform a validation study of the IBD control, of which the interim analyses showed promising results and were presented at the national Digestive Disease Days Congress. New research projects are started in this year.

6 Future perspectives

The project IBDREAM 2.0 will lead to further improvements and enlargement of IBDREAM. A ready-made IBDREAM starterskit will be made available for all academic and non-academic hospitals in the Netherlands, enabling a quick implementation of IBDREAM in new hospitals. Furthermore, automatic data sharing with electronical hospital files (EPD) will lead to improvement of the user-friendliness and accurate data collection. Laboratory results, medication and clinical outcomes can be straightforwardly downloaded into the database and/or vice versa. These data will be used to address relevant research questions and providing more insight in the real-life IBD care in the Netherlands. Several studies already started, amongst them studies to IBD care of the elderly patients, reducing unnecessary hospital visits in patients with longstanding remission and validating the IBD-control, a questionnaire to assess disease control from patient's perspective. The results of these studies may be used to directly improve quality of care and to evaluate whether comparable treatment results can be obtained at lower costs. With the rising number of participating patients and the longer prospective follow-up duration, more research questions can be answered in the future.

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www.ibdream.nl
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