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STUDY PROTOCOL

A Continuous Registry of Medical Record, Patient Input, and Epidemiological Data of Patients With Ulcerative Colitis: a Multicentre, Prospective, Observational Clinical Registry Study in Japan

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ABSTRACT

BACKGROUND

This registry aims to allow for a prospective non-interventional observational study of ulcerative colitis. This will facilitate monitoring of the current state of ulcerative colitis in Japan and improving the long-term disease course and adverse events associated with current treatment options.

METHODS

Inclusion of patients from five centres in Japan is planned. The study is expected to take place from July 15, 2020, to November 30, 2024. Background, demographics, and medical history/information will be collected from electronic medical records at enrolment. Medical information including medications, laboratory data, and disease activity will be collected automatically from electronic medical records throughout the study. Patient-reported quality of life data will be collected directly from patients via smartphone. Efficacy endpoints (clinical remission rate, clinical improvement rate, and endoscopic healing rate) and safety endpoints (incidence of adverse events and specific ulcerative colitis-related events) will be collected according to treatment administered. Treatment categories include no treatment, 5-aminosalicylic acids, corticosteroids, immunomodulators, immunosuppressants, anti-tumour necrosis alpha agents, cytapheresis, Janus kinase inhibitors, anti-integrin antibodies, and anti-interleukin-12/23 antibodies.

CONCLUSIONS

The dataset will include cross-sectional and longitudinal data and is expected to capture the state of ulcerative colitis in Japan. Patients will be included on a large scale, and the registry will be established automatically from electronic medical records and direct patient input, facilitating the accurate recording of medical information for patients with ulcerative colitis in Japan and minimizing limitations intrinsic to databases that require manual data entry, such as the burden on participating investigators and entry of data with errors/typos.

KEY WORDS

Japan, Registry study, Study protocol, Ulcerative colitis

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the digestive system; ulcerative colitis (UC) and Crohn's disease are the two most predominant clinical presentations [1, 2]. IBD is an important global health issue [3] as its prevalence continues to increase worldwide [4–6]. In 2015 there were 219,685 patients with UC and 70,700 with Crohn's disease in Japan alone [7].

Survey studies have shown that the time-of-onset for UC is often at a young age [8]. UC is a chronic, relapsing, and remitting inflammatory condition [9] that is characterised by diffuse mucosal inflammation and is localised to the large intestine [10]. Patients can have symptoms of rectal bleeding, diarrhoea, abdominal pain, and bowel urgency. Patients experience both the discomfort associated with these symptoms and poor quality of life (QOL) [11]. Crohn's disease is a chronic inflammatory condition in which lesions can arise anywhere from the mouth to the anus, with patients often experiencing extraintestinal complications [12]. Patients commonly present with diarrhoea, abdominal pain, rectal bleeding, fever, weight loss, and fatigue [12].

In Japan, IBD treatment options have expanded in recent years to include immunosuppressants and biologics; however, the disease remains refractory in a certain proportion of patients [13, 14]. As curative treatment options are not yet established, the goal of treatment is early induction of remission and long-term maintenance to prevent relapse [15]. Given the current therapeutic challenges and the fact that the number of patients with IBD is rising [5], there is a great need to establish optimal therapies. New drugs that limit persistent inflammation may also decrease the risk of progression to colorectal cancer, as risk is associated with persistent inflammation in patients with IBD [16].

Real-world patient data play an important role in understanding the overall picture of UC. The use of large amounts of data allows for the exploration of factors that may help to better optimise both treatment and the determination of prognosis. Such data may also help optimise the management of UC, improve patients' long-term QOL, and improve their ability to conduct normal daily activities and perform work duties or actively participate in academic life.

This registry aims to allow for a prospective non-interventional observational study. This will permit monitoring of the current state of UC in Japan, including current clinical practice, and aid with optimisation of the management of UC in patients and the improvement of their long-term QOL.

METHODS

STUDY DESIGN

One important consideration when determining how this registry should be built was to decide on the minimum, but most comprehensive, dataset necessary. To address this, an extensive literature search was performed to identify data that would be necessary for inclusion. Based on this, and taking into account the data included in the individual clinical assessment forms collected when applying to the Medical Expense Assistance System for Patients of Designated Intractable Diseases and the data included in The United Registries for Clinical Assessment and Research of the European Crohn's and Colitis Organisation, we put together a list of potential data elements. This list was then discussed with medical advisors and the final data for inclusion in the registry were selected.

Background and demographic information, as well as information related to medical care in patients with UC in Japan will be collected in this registry. Data regarding patient-reported QOL will be collected directly from patients via smartphone. This study will be conducted between July 15, 2020, and November 30, 2024, and is planned to include patients from at least five centres, each expecting to treat approximately 1,000 UC patients during the study period. These are Asahikawa Medical University Hospital; Kitasato University Kitasato Institute Hospital; Kyushu University Hospital; Shiga University of Medical Science Hospital; and Tokyo Medical and Dental University, Medical Hospital. The registry will eventually be expanded to include many institutions throughout Japan.

Patients who are definitively diagnosed with UC according to the Guidelines for the Management of Ulcerative Colitis published by Japan's Research Group for Intractable Inflammatory Bowel Disease [17], who are ≥18 years of age at the time of enrolment, and who provide written informed consent will be included in the study, regardless of UC treatment or disease severity. Patients who are considered ineligible by the principal investigator or sub-investigators will not be included in this study; no other exclusion criteria are set. All treatment decisions, including specific treatment administered, dosage, and treatment duration will be made by the attending physician.

The scientific and medical validity of this study, as well as the study ethics, were reviewed and approved by an

ethics committee at each participating institution prior to study initiation. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the Ministry of Health, Labour and Welfare's ethical policies for medical research in humans, and all applicable laws and regulations in Japan. All patients will be required to provide written informed consent prior to enrolment. This study is expected to include patients considered underage in Japan (≥18 years of age and <20 years of age). The parental rights holder or guardian of minors can decline participation of that minor by opting out with a consent withdrawal form. Details on opting out will be made public (http://cms.captool.jp/uc-registry/) in an effort to make the details of this study widely available. This study was registered with National Institute of Public Health (https://rctportal.niph.go.jp/en) on 14 July 2020 (UMIN000041103).

MEASURES

Information related to patient background, demographics, and medical history will be collected at enrolment. Medical information, including that related to each patient's care for UC, will be collected at least once every 3 months during the study. Specific information to be collected is listed in **Table 1**.

Data for the EuroQol 5 dimensions 5-level (EQ-5D-5L) and Short Inflammatory Bowel Disease Questionnaire will be collected from patients using smartphones. The EQ-5D-5L consists of an EQ-5D descriptive section and the EuroQol visual analogue scale. The descriptive system covers five aspects of QOL: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each of these has five levels of problem reporting: no, slight, moderate, severe, and extreme problems. Patients will be asked to describe their health status by checking boxes corresponding to the most relevant description for each dimension. A single-digit

Table 1 **Patient background and demographics at enrolment, and medical care endpoints over time.**

Type	Details
Patient background/ demographics	**General:** age, sex, height, body weight, history of appendectomy, current smoking status, pregnancy history **History of IBD:** family UC history, family CD history, UC onset (year and month), UC disease duration, disease progression[a], UC surgical history, UC treatment history[b], extra-intestinal manifestations[c] (yes/no, name of manifestation), anal lesions[d] (yes/no, type of anal lesion) **Other:** history of thromboembolism[e] (yes/no, type of thromboembolism), history of malignancy[f] (yes/no, type of malignancy)
Medical information	Medical exam date(s), body weight, current smoking status, pMayo, blood panel[g], faecal calprotectin, *Clostridioides difficile* infection, colonoscopies (yes/no), MES, UCEIS, disease progression[a], terminal ileum lesions, appendix lesions, dysplasia, hospitalisations (yes/no, hospitalisation reason, complications while hospitalised), intestinal complications[h] (yes/no, type), surgeries[i] (yes/no, procedure type, surgical indication), treatments (yes/no, drug names, prescribed doses), reasons for dose or interval changes, reasons for change in therapeutic agent, adverse events, infectious diseases[j], extra-intestinal manifestations[c], anal lesions[d], thromboembolism[e], malignancies[f], haematological malignancies[k], pregnancies, childbirth, vaccinations[l], serological assessments[m], tuberculosis tests[n], EQ-5D-5L, SIBDQ

CD, Crohn's disease; EQ-5D-5L, EuroQol 5 Dimension 5 Level; IBD, irritable bowel syndrome; MES, Mayo endoscopic score; pMayo, partial Mayo; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; UC, ulcerative colitis; UCEIS, ulcerative colitis endoscopic index of severity.

[a] Proctitis, Left-sided colitis, pancolitis, right-sided colitis, non-specific, other.

[b] Includes mesalazine, salazosulfapyridine, prednisolone, tacrolimus, infliximab, adalimumab, golimumab, tofacitinib, ciclosporin, vedolizumab, ustekinumab, azathioprine, mercaptopurine, leukocyte apheresis (including granulocyte and monocyte adsorption apheresis).

[c] Includes peripheral joint involvement, spondyloarthritis (including ankylosing spondylitis and sacroiliitis), involvement of the skin (erythema nodosum, pyoderma grangrinosum, other), involvement of the eyes (iritis, scleritis), oral aphtha, primary sclerosing cholangitis, pancreatitis, lungs, other.

[d] Includes anal fistula, perianal abscess, anal stricture, other.

[e] Includes cardiovascular events, deep-vein thrombosis, pulmonary infarction/pulmonary embolism, portal vein thrombosis, myocardial infarction, cerebral infarction, catheter thrombosis, other.

[f] Includes lung cancer, gastric cancer, colorectal cancer, liver cancer, breast cancer, prostate cancer, other.

[g] Includes haemoglobin, albumin, platelets, creatinine, aspartate aminotransferase, alanine aminotransferase, bilirubin, alkaline phosphatase, gamma-glutamyl transferase, total protein, total cholesterol, iron, ferritin, transferrin, transferrin saturation, 25-(OH)-D, vitamin B12, folic acid, c-reactive protein, white blood cell, white blood cell differential, red blood cell, erythrocyte sedimentation rate.

[h] Includes toxic megacolon, serious bleeding, perforation, thrombosis, infectious disease, other.

[i] Includes (sub) total colectomy, residual rectal resection, Ileoanal (canal) anastomosis, temporary colostomy/permanent colostomy, stoma closure, other; surgical indications: toxic megacolon, bleeding, carcinoma/dysplasia complications, other.

[j] Includes herpes zoster, *Pneumocystis jirovecii* pneumonia, bacterial pneumonia, skin infection, urinary tract infection, other.

[k] Includes leukaemia, malignant lymphoma, multiple myeloma, myelodysplastic syndrome, other.

[l] Includes influenza, pneumococcus, herpes zoster.

[m] Includes hepatitis A, hepatitis B, hepatitis C, cytomegalovirus, Epstein-Barr virus, mumps, rubella, measles, chicken pox, human immunodeficiency virus.

[n] Includes X-ray imaging, computerized tomography scan, tuberculin reaction, interferon gamma release test (QuantiFERON-TB or T-spot).

number will be derived for each dimension, and the patient's health status will be described using the resulting five-digit number. The EuroQol visual analogue scale is a vertically aligned scale patients can use to report their self-rated health status, with its extremes labelled 'The best health you can imagine' and 'The worst health you can imagine'. The EuroQol visual analogue scale gives a quantitative index of health status, reflecting patients' own assessments.

The Short Inflammatory Bowel Disease Questionnaire is a survey structured around 10 questions that grade QOL with four sub-scores for 'bowel symptoms', 'emotional function', 'systemic symptoms', and 'social function', which are then evaluated in seven steps, from 1 ('severe problem') to 7 ('no problem at all'). The scores then range from 10 (poorest score) to 70 (optimal score).

DATA COLLECTION METHODS

Written informed consent will be obtained by the lead investigator or sub-investigator at each study site and patients will be enrolled after verifying that they are eligible for the study. Subsequent data collection will occur by one of two methods, depending on whether the study site has an on-boarded Standardized Structured Medical Information eXchange 2 (SS-MIX2) server [18].

The process for data collection at study centres that do not have SS-MIX2 software is shown in **Fig 1a**. The lead investigator or a sub-investigator at the study centre will input medical information (medical exam and treatment) for each enrolled patient into a template specially prepared for this study in their electronic charts. The data entered into the template will then be collected and saved in an external storage device (a site server) at the study centre. Subsequently, the data will be saved in the Centre Server operated by Osaka University Hospital. Inputs for QOL surveys will be performed by patients themselves using their own smartphone. These data will be collected and stored in an electronic patient-reported outcomes database at Accelight Technologies Inc. (Tokyo, Japan). Finally, data collected in the Centre Server and electronic

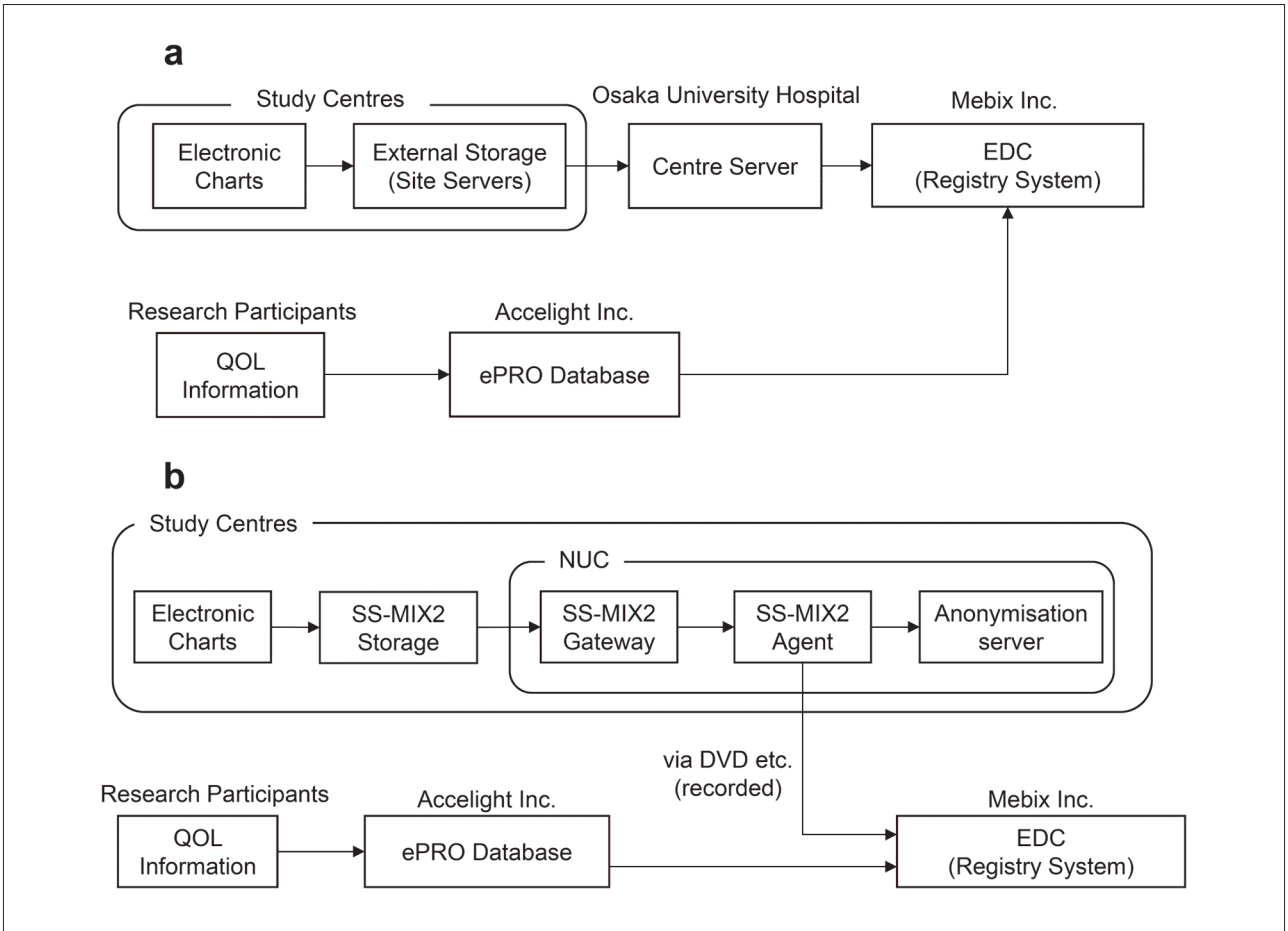

Fig. 1 **Process for data collection at (a) study centres that do not have SS-MIX2 software and (b) study centres that have SS-MIX2 software.**

EDC, Electronic Data Capture; ePRO, electronic patient-reported outcomes; NUC, Next Unit of Computing; QOL, quality of life; SS-MIX2, Standardised Structured Medical Information eXchange 2 software.

patient-reported outcomes database will be entered into the Electronic Data Capture (registry system) managed by Mebix, Inc. (Tokyo, Japan).

The process for data collection at study centres that have on-boarded SS-MIX2 software is shown in **Fig. 1b**. The lead investigator or a sub-investigator at the study centre will input medical information (medical exam and treatment) for each enrolled patient into a template specially prepared for this study in their electronic charts. The data entered into the template will then be saved in a Next Unit of Computing PC installed at the study centre. Each study centre will then write the entered information into DVDs or other storage devices on an annual basis. The stored data will then be provided to Mebix, Inc. Mebix, Inc. will synchronise and gather the patient's information from the DVDs or other storage devices provided by the study centre into the registry system. Inputs for QOL surveys will be done by patients themselves using their own smartphone. These data will be collected and stored in an electronic patient-reported outcomes database at Accelight Technologies Inc. Finally, data collected in the electronic patient-reported outcomes database will be entered into the registry system managed by Mebix, Inc.

Patient data will be anonymised prior to providing to third parties from the study centres. For data collected from study centres that have not on-boarded the SS-MIX2 software and for QOL data, anonymity will be ensured by assigning numbers to each study participant. Mebix, Inc. will govern all anonymised data. For data collected from study centres that have on-boarded the SS-MIX2 software, electronic medical records will be sent to a Next Unit of Computing and anonymised prior to storage.

OUTCOME ASSESSMENTS

Patient background and demographic information at enrolment, and medical care information over time (as listed in **Table 1**) will be analysed. Medical care information will be collected at every clinic visit or at least once every 3 months. Efficacy endpoints include clinical remission rate [19], clinical improvement rate, and endoscopic healing rate (all defined in **Table 2**) according to treatment administered. Safety endpoints include the incidence of adverse events, infectious disease, extraintestinal manifestations, anal lesions, thromboembolism, malignancy, and haematological malignancy according to treatment administered. Prescription continuation rate according to treatment administered will also be included as an exploratory endpoint. The following categories of treatment will be included in the analyses: no treatment, 5-aminosalicylic acids, corticosteroids, immunomodulators, immunosuppressants, anti-tumour necrosis alpha agents, haemocyte component apheresis, Janus kinase inhibitors, anti-integrin antibodies, and anti-interleukin-12/23 antibodies.

SAMPLE SIZE CALCULATION

The sample size in this study was set based on feasibility rather than statistical methods. The sample size was set at 5,000 patients in anticipation of participation by five centres with approximately 1,000 UC patients per centre.

STATISTICAL METHODS

The efficacy analysis set will include all enrolled patients who have been prescribed at least one of the drugs specified for the study endpoints and for whom efficacy evaluations are available. The safety analysis set and continued treatment analysis set (exploratory endpoint) will include all enrolled patients who have been prescribed at least one of the drugs specified for the study endpoints.

Summary statistics, including the mean, median, maximum frequency, standard deviation, range, quartile, and number of observed values will be calculated. Two-sided

Table 2 Definitions of clinical remission, clinical improvement, and endoscopic healing to be used in this study.

Parameter	Definition
Clinical remission [19]	Meets all of the conditions below: 1) Stool frequency subscore of ≤1 2) Rectal bleeding subscore of 0 3) Physician's global assessments score of 0
Clinical improvement	An improvement of ≥2 points from baseline by pMayo score (stool frequency, rectal bleeding, and physician's global assessment total for all subscores)
Endoscopic healing	Endoscopic subscores (MES) of ≤1

MES, Mayo endoscopic subscore; pMayo, partial Mayo.

95% confidence intervals will be used. Data on background patient characteristics will be summarised cumulatively, while other data will be summarised annually. Safety events for prescription drugs will be reported from the starting date of the prescription to the last prescription date plus the number of prescription days plus 28 days. Drug efficacy (clinical remission rate, clinical improvement rate, endoscopic remission rate) and rate of continuation will be analysed from baseline to Month 3, Month 6, and then every 6 months. Missing data will not be imputed. All statistical analyses will be performed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

DISCUSSION

This prospective UC disease registry will not limit inclusion to the use of a specific drug, type of pharmacotherapy, or disease severity. Rather, data on patient background and demographics as well as medical care over time will be included, as well as QOL assessments for some patients. Included patients will be ≥18 years of age at the time of consent and will have confirmed UC. As such, the registry has been structured to allow researchers to evaluate the current state of UC and long-term patient outcomes in Japan.

This is the first time a registry that will automatically and directly collect electronic medical records and patient-reported outcomes data from patients within the indication of UC has been established.

Patients with UC experience not only physical symptoms such as rectal bleeding, diarrhoea, abdominal pain, and bowel urgency, but also uneasiness related to these symptoms [11]. This uneasiness can negatively influence employment opportunities and work productivity, restrict a patient's social life, and impede their ability to participate in recreational activities [20–24]. Importantly, the effects of UC may harm a patient's ability to build and maintain strong relationships with others, which then makes it difficult for them to form close bonds, evoking a sense of loneliness and depression [20, 21, 25]. Several studies have reported that the presence and severity of physical symptoms have a great impact on a patient's capabilities and sense of happiness, as well as their health-related QOL [26, 27]. Therefore, treatments that improve a patient's clinical assessments are also expected to improve health-related QOL; this has, in fact, been demonstrated in several clinical studies [28–30]. Patient-reported outcome data on QOL (EQ-5D-5L and Short Inflammatory Bowel Disease Questionnaire) will be collected at least once every 6 months for patients enrolled in this study and is expected to help evaluate the level of QOL improvement according to treatment. Importantly, this dataset will be made widely available to academic researchers (although it will only be available in Japanese).

This study will have several strengths. First, as this is the first endeavour, within the indication of IBD, to establish a registry that will automatically and directly collect electronic medical records and patient-reported outcome data from patients, we expect the registry to have the potential to impact UC management in Japan. The collection of data directly from electronic medical records is expected to reduce the burden on participating investigators and help prevent errors or typos in data entry, which would otherwise be expected in databases that require manual data entry. This study will include UC patients on a large scale, given that we anticipate the inclusion of about 5,000 patients. The data collected will provide important information regarding UC treatment in Japan, and the background information collected will include a wide range of potential epidemiological risk factors. The dataset will be composed of cross-sectional and longitudinal data. Finally, because there were no stipulations on treatment, no stringent inclusion criteria, and no exclusion criteria applied, we expect that a diverse array of UC patients will participate in this study.

This study will have several limitations. First, while the collection of patient-reported outcome data on QOL will be included in the study, collection will be limited to patients who can input their information into their smartphone. Data from patients who do not own a smartphone or those who are incapable of inputting data into a smartphone will not be included. As such, the QOL data collected from this study may not be fully representative of the overall population of patients with UC. However, it should be noted that around 70% of the Japanese population owns a smartphone [31] and given that the UC patient population tends to be younger, we expect smartphone usage to be even higher in the study population. Thus, we expect the impact on the generalisability of QOL outcomes to be minor. Second, participation will be limited to approximately five large hospitals around Japan that were selected on the basis of a large number of UC patients (~1,000), greater medical care resources, and a high level of expertise. While the drugs used to treat UC patients across institutions in Japan are similar, the characteristics of the enrolled patient population may not match those of patients treated at hospitals with fewer medical care resources and less expertise.

Therefore, the medical data collected from this study may not be fully representative of the overall UC patient population. Third, patients who are admitted to other hospitals or visit their neighbourhood clinics cannot be followed up. Therefore, if attrition bias is present, it can compromise the validity, reliability, and generalizability of the study results. Finally, this study was designed to collect and input data into electronic charts which will facilitate the creation of a large-scale registry of routine medical care patterns. However, automatic data checks for logic correction and visual confirmations will not be performed. As such, the lack of quality control may impact the quality of the data.

Regarding the method used to determine the data collection items for this study, we believe we have developed a plan that will ensure this registry covers the minimal potential epidemiological risk factors required to facilitate pooled analyses and answer important clinical questions. We expect that this registry of long-term data from a large patient sample with UC will generate important insights on the characteristics of patients who are highly responsive to UC treatment and of those who are less responsive. This is expected to further lead to the generation of information on treatment strategies in UC patients and contribute to the provision of optimal medical care for these patients.

CONFLICTS OF INTEREST

KM has received full support for the current study from Pfizer Japan Inc.; grants and honoraria from Mitsubishi Tanabe Pharma, AbbVie Inc., EA Pharma Co., Ltd., Kyorin Pharmaceutical Co., Ltd., Mochida Pharmaceutical Co., Ltd., ZERIA Pharmaceutical Co., Ltd., Kissei Pharmaceutical Co., Ltd., Nippon Kayaku Co., Ltd., and JIMRO Co., Ltd; and honoraria from Takeda Pharmaceutical Co., Ltd., Pfizer Inc, Janssen Pharmaceutical K.K., Gilead Sciences, and Eli Lilly Japan K.K. SH has received full support for the current study from Pfizer Japan Inc.; and honoraria from AbbVie GK, Mochida Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co., Ltd., EA Pharma Co. Ltd., and Kissei Pharmaceutical Co., Ltd. KA has received full support for the current study from Pfizer Japan Inc.; and honoraria from Nippon Kayaku Co. Ltd., Janssen Pharmaceutical K.K., Mitsubishi Tanabe Pharma Corporation, Takeda Pharmaceutical Co., Ltd., AbbVie GK., JIMRO Co., Ltd., EA Pharma Co. Ltd., AYUMI Pharmaceutical Corporation, Mochida Pharmaceutical Co., Ltd., Aspen Japan K.K., Pfizer Japan Inc., Eli Lilly Japan K.K., Alfresa Pharma Co. Ltd., Sandoz K.K., and KYORIN Pharmaceutical Co., Ltd. YT has received full support for the current study from Pfizer Japan Inc. TT has received full support for the current study from Pfizer Japan Inc.; and grants from Mitsubishi Tanabe Pharma Corporation, Zeria Pharmaceutical Co., Ltd., AbbVie Inc, Mochida Pharmaceutical Co., Ltd., and EA Pharma Co., Ltd. HO has received full support for the current study from Pfizer Japan Inc.; and honoraria from Miyarisan Pharmaceutical Co. Ltd., Fujifilm Medical Co., Ltd., Terumo Corporation, FANCL Corporation, Jansen Pharmaceutical, Mitsubishi-Tanabe Pharmaceutical, Takeda Pharmaceutical, EA Pharma, JIMRO, Pfizer Japan Inc., and Mochida Pharmaceutical. TY has received full support for the current study from Pfizer Japan Inc. AA has received full support for the current study from Pfizer Japan Inc., and honoraria from Takeda Pharmaceutical Company and Miyarisan Pharmaceutical Company. YS has received full support for the current study from Pfizer Japan Inc. TM has received full support for the current study from Pfizer Japan Inc.; honoraria from Jansen Pharmaceutical, Mitsubishi-Tanabe Pharmaceutical, Takeda Pharmaceutical, EA Pharma, JIMRO, Kyorin Pharmaceutical, Viatris, Pfizer Japan, Mochida Pharmaceutical, Kissei Pharmaceutical, and Nippon Kayaku; and participates on the Data Safety Monitoring Board or Advisory Board of Jansen Pharmaceutical and Takeda Pharmaceutical. YI has received full support for the current study from Pfizer Japan Inc. TS has received full support for the current study from Pfizer Japan Inc. TK has received full support for the current study from Pfizer Japan Inc.; grants from JMDC Inc., Gilead Sciences, Inc., Eli Lilly Japan K.K., Ferring Pharmaceuticals, Bristol-Myers Squibb, Google Asia Pacific Pte. Ltd; grants and honoraria from Zeria Pharmaceutical Co., Ltd., JIMRO Co., Ltd.; grants, honoraria, and payment for expert testimony from Janssen Pharmaceutical K.K., Takeda Pharmaceutical Co., Ltd., Activaid, Nippon Kayaku Co., Ltd., Alfresa Pharma Corporation, Kyorin Pharmaceutical Co., Ltd., Mitsubishi Tanabe Pharma Corporation, AbbVie GK, Pfizer Japan Inc.; grants and payment for expert testimony from EA Pharma Co., Ltd., Mochida Pharmaceutical Co., Ltd.; payment for expert testimony from KISSEI Pharmaceutical Co., Ltd.; and honoraria from Thermo Fisher Diagnostics K.K.

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