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Ulcerative colitis outcomes research using patient-focused registry in Japan: protocol for an observational prospective cohort study of YOURS (YOU and Ulcerative colitis: Registry and Social network) Registry

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TITLE

Ulcerative colitis outcomes research using patient-focused registry in Japan: protocol for an observational prospective cohort study of YOURS (YOu and Ulcerative colitis: Registry and Social network) Registry

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ABSTRACT

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease that mainly affects the colon in young patients. Typical symptoms of UC are bloody diarrhea and fecal urgency, which disturb the quality of life (QOL) of patients, and intractable UC leads to hospitalization and colectomy. To improve relevant outcomes such as symptoms, QOL and colectomy, many clinical questions need to be resolved regarding what the ideal lifestyle, psychosocial burden and optimal practice patterns are. In this YOURS study, based on a patient-focused registry, we will investigate the effect of lifestyle, psychosocial factors and practice patterns on patient-reported outcomes (PRO), hospitalization rate and colectomy rate in Japanese patients with UC.

Methods and analysis

For this prospective cohort study, we recruited 2006 patients from five hospitals (Tokyo and Chiba; May 2018–January 2019). Using a patient-focused registry, patients will be able to access their own data and compare them with summarized data from all patients on the website. At baseline, patients will answer a questionnaire regarding lifestyle (diet, exercise, sleep and work), psychosocial factors (stress, depression, social support, etc.) and PRO (symptoms and QOL). Information on practice patterns (eg, medications, endoscopy frequency) will be collected from electronic medical records. Gaps between patients' needs and healthcare professionals' practice will be identified. Follow-up surveys will be conducted periodically for approximately three years. Research questions suggested by patients and healthcare professionals may be used in subsequent surveys. Results from the YOURS study will demonstrate optimal UC management strategies to improve relevant outcomes, and the YOURS patient-focused registry will provide patients with an opportunity to learn from other patients.

Ethics and dissemination

The study was approved by the ethics committees of five investigational sites before starting the study. The results will be submitted to journals. (UMIN Clinical Trials Registry: UMIN000031995)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The YOURS study is a large-scale, long-term, prospective observational study to explore optimal ulcerative colitis management for improving relevant outcomes using data collected by a patient-focused registry.
- The YOURS study reflects the real clinical setting because any concomitant drugs and therapies are allowed.
- The YOURS study can be expanded for subsequent surveys because patients and healthcare professionals can ask research questions not otherwise included in the survey.
- Patients will be able to access their own data and compare them with summarized data from all patients on the website beyond the YOURS study.
- All investigational sites are located within one region of Japan, which may affect the study results, especially because of lifestyle and psychosocial factors.

KEY WORDS

Cohort study; Colitis, ulcerative; Patient outcome assessment; Patient focused registry; Quality of life.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease with no curative treatment. It mainly affects the colon and is associated with bloody diarrhea and fecal urgency as typical symptoms.[1] Aberrant immunity in the gut is considered to be involved in the pathogenesis of UC,[2] however, the etiology of UC is not fully understood. Ulcerative colitis are increasing around the world, especially in Asia, including Japan.[3-5] The prevalence of UC has been reported to range from 5.3 to 63.6 per 100 000 people in Asia and from 37.5 to 238 per 100 000 people in North America,[1] and differs between regions, with the prevalence in Japan reported as approximately 100 per 100 000 people in 2013.[5]

The onset of UC often has a major influence on patients' quality of life (QOL), and intractable UC can lead to hospitalization and colectomy. Patients need to manage UC throughout their lives with both self-management and support from healthcare professionals (HCPs) to avoid unwanted clinical outcomes, including relapse/exacerbation, hospitalization, and colectomy, as well as to improve patient-reported outcomes such as QOL. To support self-management, the need for patient-focused registries has recently been emphasized. Unlike traditional patient registries, patient-focused registries have interactive functions such as patient involvement in the development of research questions that the registry needs to address, feeding back data to patients, and data-sharing for both patients and HCPs.[6] Although the concept of patient-focused registries is promising, only a few patient-focused registries exist for inflammatory bowel disease (IBD), mainly in the United States, such as ImproveCareNow[7] for pediatric and adolescent patients and IBD Qorus[8] for adult patients.

In establishing a new patient-focused registry (YOu and Ulcerative colitis: Registry and Social network [YOURS] registry) for Japanese patients, we identified four main factors/challenges to the improvement of patient outcomes: (1) lifestyle, (2) psychosocial

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3 factors, (3) practice patterns and (4) gaps between patients' needs and HCPs' practice
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5 (Figure 1).
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10 First, there has been much discussion and debate about the optimal lifestyle (diet, exercise,
11 sleep and work) for UC management. In particular, diet is a critical issue for both patients
12 and their HCPs. Although a large-scale study has reported that the relationship between diet
13 and relapse is a major interest of patients with IBD and their HCPs,[9] only two exploratory
14 studies have examined the relationship.[10, 11] However, the results from these studies were
15 not consistent.
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24 Second, psychosocial factors including stress, depression and social support may affect
25 clinical outcomes in UC. Approximately half of patients with IBD have low QOL and
26 depression,[12] and one third of patients are reported to feel stigmatized.[13] It remains
27 unknown how these psychosocial factors affect disease course.
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35 The third challenge is practice patterns. The Selecting Therapeutic Targets in Inflammatory
36 Bowel Disease (STRIDE) program, published in 2015 by IBD specialists, recommends
37 setting concrete treatment goals as part of a "Treat to Target" strategy.[14] The agreed
38 treatment goals for UC were clinical remission (defined as resolution of rectal bleeding and
39 diarrhea/altered bowel habit) and endoscopic remission (based on endoscopic findings).
40 However, achievement of these treatment goals may be accompanied by decreased QOL
41 due to frequent colonoscopies or side effects caused by immune suppression. Optimal
42 disease monitoring and treatment need to be clarified.
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53 The last challenge is gaps between patients' needs and HCPs' practice. A previous survey
54 has identified important differences between patients and HCPs in their perception of the
55 impact of UC symptoms on patients' lives, suggesting that HCPs may underestimate the
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3 effect of UC symptoms on patients.[15] However, the effect of perception gaps on patient
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5 outcomes is unknown.
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9 The YOURS study is an observational prospective cohort study in patients with UC in Japan
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11 that aims to clarify how these four challenges affect relapse/exacerbation, hospitalization,
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13 colectomy and patient-reported outcomes such as QOL.
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METHODS AND ANALYSIS

Study design

The YOURS study is an observational prospective cohort study with a 3-year follow-up being conducted at five investigational sites in Japan. Patient registration started in May 2018 and ended in January 2019. As of 11 January, 2019, 2006 patients have been enrolled.

The study is being conducted in compliance with the Declaration of Helsinki, Ethical Guidelines for Medical Research on Humans, Ministry of Education, Culture, Sports, Science and Technology of Japan and Ministry of Health, Labour and Welfare of Japan, and all applicable laws and guidelines. Written informed consent will be obtained from all patients.

The study is registered at the University hospital Medical Information Network (UMIN) Center Clinical Trials Registry (UMIN000031995).

Study population and sample size

Patients diagnosed with UC, as defined by the "Evidence-based Clinical Practice Guidelines for Inflammatory Bowel Disease",^[5] who are ≥ 16 years of age at informed consent and are attending the investigational sites are eligible for enrolment.

The sample size was determined by considering the feasibility of enrolling patients.

Outcome measures and survey items

Relapse/exacerbation, hospitalization, colectomy and patient-reported outcomes such as QOL will be assessed as main outcomes. However, all survey items may also be assessed as outcomes. All surveys will be conducted in Japanese and will include standard, validated questionnaires for most measures of lifestyle, psychosocial factors and symptoms.

At the initial survey, patients will complete written questionnaires with demographic, lifestyle, psychosocial and symptom questions (Table 1, Figure 2). Following the initial survey,

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3 patients will complete a brief symptom survey including psychosocial and symptom questions
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5 by smartphone application, email, phone or written questionnaire every three months, and a
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7 follow-up survey including lifestyle, psychosocial and symptom questions by written
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9 questionnaire every year for three years (Table 1, Figure 2). Patients who maintain remission
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11 for at least 90 days will complete a special survey by written questionnaire at three months
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13 from the time of the initial survey, which includes lifestyle questions focusing on diet, exercise
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15 and stress management as strategies to prevent relapse (Table 1, Figure 2). Remission is
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17 defined as a stool frequency score of 0 or 1 and a rectal bleeding score of 0 (two-item
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19 patient-reported outcome; Table 2).[16] Patients will have the opportunity to provide their
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21 own research questions at the initial survey and all follow-up surveys. If the research
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23 questions are feasible for this study, they will be included in the subsequent surveys within
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25 the YOURS study.
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31 **Table 1.** Survey items/questionnaires

	Category	Item (questionnaire)
<i>By patients</i>		
Initial survey	Patient information	Body height, weight, UC history, appendectomy, medical history including malignant tumor, anal fistula and perianal abscess, family history of inflammatory bowel disease, vaccination history, smoking history, education level, economic status and pregnancy history
	Lifestyle	Exercise (IPAQ), sleep (PSQI) and Labor productivity (WPAI)
	Psychosocial factors	Social support (mMOS-SS), medication adherence (ASK-12), comprehensive QOL (QGEN®10 survey), disease-specific QOL (SIBDQ), depression/anxiety (HADS), stress (JPSS) and disease-specific QOL (QDIS®)
	Symptoms	Stool frequency and rectal bleeding (PRO-2), pain (NRS) and fatigue (FACIT-F)
	Others	Research questions not included in this survey
Special survey (in patients in remission for at least 90 days, at 3	Lifestyle	Diet (BDHQ)
	Others	Diet, exercise and stress management strategies to prevent relapse

months from the time of initial survey)		
Symptom survey (every 3 months)	Psychosocial factors Symptoms	Disease-specific QOL (QDIS®) Stool frequency and rectal bleeding (PRO-2)
Follow-up survey (every year)	Lifestyle	Sleep (PSQI) and Labor productivity (WPAI)
	Psychosocial factors	Medication adherence (ASK-12), comprehensive QOL (QGEN®10 survey), disease-specific QOL (SIBDQ), depression/anxiety (HADS) and stress (JPSS)
	Symptoms	Stool frequency and rectal bleeding (PRO-2), pain (NRS) and fatigue (FACIT-F)
	Others	Research questions not included in this survey
By HCP		
HCP survey (initial)	-	Observations related to lifestyle guidance for diet, exercise and strategies to avoid stress; research questions not included in this survey
Medical record survey (initial only)	Patient information	Age, sex, worst disease extent (eg, pancolitis, left-sided colitis, extensive colitis), extra-intestinal complications and treatment history
Medical record survey (initial, 3 months from the initial survey, every year)	Medical information	Partial Mayo score, medication, observation of endoscope and pathologic observation, <i>Clostridium difficile</i> infection, blood exam, calprotectin in stool, hospitalization, colectomy, pregnancy, adverse events and malignancy

Abbreviations: ASK-12,[17-20] Adherence Starts with Knowledge-12; BDHQ,[21, 22] Brief-type self-administered Diet History Questionnaire; FACIT-F,[23-25] Functional Assessment of Chronic Illness Therapy - Fatigue; HADS,[26-29] Hospital Anxiety and Depression Scale; HCP, healthcare professional; IPAQ,[30, 31] International Physical Activities Questionnaire; JPSS,[32, 33] Japanese version of the Perceived Stress Scale; mMOS-SS,[34-36] modified Medical Outcomes Study Social Support Survey; NRS,[37] Numerical Rating Scale; PRO-2,[16] two-item patient-reported outcomes; PSQI,[38, 39] Pittsburgh Sleep Quality Index; QDIS®,[40] Quality of life Disease-specific Impact Scale; QGEN®,[41] Quality of life GENERAL; QOL, quality of life; SIBDQ,[42-44] Short version of Inflammatory Bowel Disease Questionnaire; UC, ulcerative colitis; WPAI,[45, 46] Work Productivity and Activity Impairment questionnaire.

Table 2. Definition of stool frequency score and rectal bleeding score in PRO-2

Score	Definition
Stool frequency	
0	Normal number of stools
1	1-2 stools more than normal
2	3-4 stools more than normal
3	5 or more stools more than normal
Rectal bleeding	
0	None

1	Streaks of blood with stool less than half the time
2	Obvious blood with stool most of the time
3	Blood alone passed

Abbreviation: PRO-2, two-item patient-reported outcomes.

In the HCP survey, HCPs will complete written questionnaires about their guidance to patients with remission regarding diet, exercise and stress management in order to prevent relapse. Answers from patients and HCPs will be compared and any gaps in the perception of the ideal lifestyle to prevent relapses will be identified and explored. In addition, HCPs will collect patients' medical information such as medication use, blood exams, stool exams, endoscopic findings, pathologic findings, hospitalizations, colectomy status and adverse events (throughout the study) from electronic medical records at all surveys (Table 1, Figure 2).

Data management

The YOURS study uses an electronic data capture (EDC) system to register patients, collect survey answers and create a database, which can be accessed securely by investigators who have received appropriate training. The principal investigators are responsible for ensuring data quality.

Patient-focused registry

Patients will be provided written feedback on their data compared with the other patients participating in the YOURS study. Moreover, patients can use the website for reviewing their data over time, comparing with others, and sharing with HCPs, provided the patients have requested access and agreed to the transfer of their data from the database to the website with written informed consent (Figure 3). The website is operated by a third-party general incorporated association, the Patient Driven Academic League (PeDAL), which was founded by a patient who underwent renal transplantation. The use of PeDAL was approved by the YOURS steering committee.

Statistical analysis

Analysis groups will be determined for each outcome measure and survey item. The baseline data on demographics, lifestyle, psychosocial factors, practice patterns, and gaps between patients' needs and HCPs' practice will be summarized. The following statistical analyses to clarify the association of these baseline data with relapse/exacerbation, hospitalization, colectomy, and patient-reported outcomes such as QOL will be conducted.

Logistic regression analysis or Cox proportional hazard model will be used for analysis of binary variables. Linear regression analysis will be used for analysis of continuous variables. Multilevel analysis may be used for considering differences between investigational sites. Confounding factors will be adjusted appropriately for all analyses.

Interim database locks and interim analyses are planned as follows: initial survey, special survey at three months from the time of the initial survey, and follow-up surveys at two and three years after the initial survey.

Patient and public involvement statement

We will collect research questions from both patients and HCPs from surveys in the YOURS study. If the research questions are feasible for this study, they will be included in the subsequent surveys within the YOURS study.

ETHICS AND DISSEMINATION

The YOURS study is sponsored by Takeda Pharmaceutical Company Limited (Tokyo, Japan) and advice on the study plan was obtained from the Japanese Society for Inflammatory Bowel Disease. The study is managed by six joint research organizations, including Takeda and five investigational sites: Tokyo Medical and Dental University, Medical Hospital (Tokyo, Japan); Kitasato University Kitasato Institute Hospital (Tokyo, Japan); Kyorin University Hospital (Tokyo, Japan); Tokyo Women's Medical University Hospital (Tokyo, Japan); and Toho University Sakura Medical Center (Chiba, Japan), and was approved by the ethics committees of five investigational sites before starting the study. The YOURS study has a steering committee consisting of medical experts conducting the study, representatives of the joint research organizations and clinical epidemiology experts. The roles of the steering committee are to supervise the overall study operation, provide medical expertise guidance, ensure the scientific quality of the study is at a high level and update the protocol appropriately when needed. The results will be submitted to journals for publication.

DISCUSSION

The YOURS patient-focused registry has been established with four primary goals: (1) develop a platform to share clinical knowledge and patient experience, (2) define optimal care for UC, (3) fill gaps between patients' needs and HCPs' practice and (4) improve relevant outcomes. In conjunction with the YOURS registry, the YOURS study will investigate how four main challenges (lifestyle, psychosocial factors, practice patterns and gaps between patients' needs and HCPs' practice) affect relapse/exacerbation, hospitalization, colectomy and patient-reported outcomes such as QOL.

Based on the YOURS study results, we plan to create a booklet regarding the ideal lifestyle and psychosocial factors to help patients avoid unwanted clinical outcomes. Although booklets are a preferred adjunct source of information for patients with IBD and it is important to distribute booklets, the same information will also be disseminated in other ways, such as websites, as needed.[47] The YOURS study booklet will include specific information on diet, exercise, sleep, work, stress, depression and social support. Moreover, if we identify any gaps between patients' needs and HCPs' practice regarding lifestyle guidance, we will include that information in the booklet as background information. We expect that the booklet will facilitate sharing information between patients and HCPs, thereby helping to bridge gaps between patients' needs and HCPs' practice.

The YOURS registry will serve as a patient-centered learning environment and provide integrated information about patients' experiences and clinical data for supporting management decisions. Other patient-focused registries for IBD, such as ImproveCareNow[7] for pediatric and adolescent patients and IBD Qorus[8] for adult patients, have successfully promoted sharing information and learning from other patients to improve IBD treatment.[48] The YOURS registry focuses not only on practice patterns, but also on a more comprehensive management of UC, including lifestyle, psychosocial factors and gaps between patients' needs and HCPs' practice. In addition, YOURS is the first comprehensive

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3 registry available for Japanese adult and older adolescent (≥ 16 years old) patients with UC.
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5 Importantly, although the YOURS registry was originally developed for the YOURS study, the
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7 registry will not be used solely for this study. Patients will be able to access their own data on
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9 the website (by smartphone application or computer) to review their symptoms over time,
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11 compare with others, self-manage their UC, and make shared decisions with their HCPs.
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16 The YOURS study is a large-scale, long-term, prospective observational study without any
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18 prohibited concomitant drugs and therapies, thereby reflecting real clinical settings. However,
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20 as all investigational sites are located in Tokyo or Chiba (which is near Tokyo) in Japan, the
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22 applicability of the study results to other locations may be affected by lifestyle and
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24 psychosocial factors influenced by regional, country, and/or cultural differences. The YOURS
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26 study can potentially be expanded in subsequent surveys within the study because patients
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28 and HCPs can ask research questions not otherwise included in the survey.
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33 In conclusion, the YOURS study provides an important opportunity to clarify how challenges
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35 such as lifestyle, psychosocial factors, practice patterns and gaps between patients' needs
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37 and HCPs' practice affect clinical outcomes in patients with UC in Japan. We anticipate that
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39 results from the YOURS study will demonstrate optimal UC management strategies to
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41 improve relevant outcomes. In addition, the YOURS patient-focused registry will enable
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43 investigators to learn from both patients and HCPs and, importantly, for patients to learn from
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45 each other.
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Authors' contributions

All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. H Yamazaki, K Matsuoka, J Fernandez and S Fukuhara were involved in the study design. K Matsuoka, T Hibi, M Watanabe and T Hisamatsu are investigators and have collected the data in the study.

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Disclaimer

Takeda Pharmaceutical Company Limited has been or will be involved in the study design, data collection, data analysis, and preparation of the manuscript.

Competing interests

H Yamazaki has no conflicts of interest to declare. K Matsuoka has received grants and personal fees from Sekisui Medical, AbbVie, and Thermofisher Scientific, grants from Alfresa Pharma Corporation, personal fees from Mitsubishi-Tanabe Pharma, Eisai, Kyorin

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9 Pharmaceutical Company Limited and owns restricted stocks of Takeda Pharmaceutical
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Patient consent

Obtained.

Ethics approval

The study was approved by the ethics committees of five investigational sites.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

As enrolment has only recently finished and no analysis has been conducted yet, there are no data that can be shared at this time.

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FIGURE LEGENDS

Figure 1. Factors and outcomes assessed in the YOURS study.

All 4 factors can contribute to all 4 outcomes.

HCP, healthcare professional.

Figure 2. Study design.

Surveys on the left side are for patients, and surveys on the right side are for HCPs.

All surveys were completed by written questionnaires, except for the symptom survey, which could be completed by smartphone application, email, phone, or written questionnaire. The special survey at 3 months from the time of initial survey was only completed by patients who maintained remission for at least 90 days.

HCP, healthcare professional.

Figure 3. Scheme of the YOURS patient-focused registry

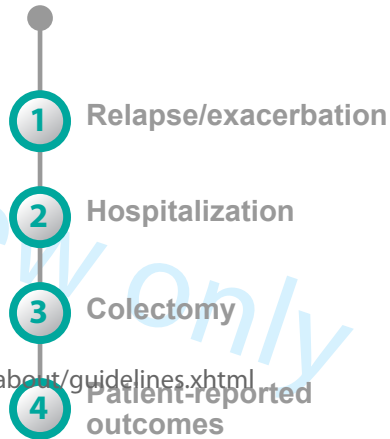
- a) Survey answers and medical records will be collected from patients and HCPs by written questionnaire, smartphone application, email, or phone, and stored in the YOURS study database.
- b) Patients can use a website for reviewing their own data over time if the patients have requested access and agreed to the transfer of their data to the website.
- c) Patients can also use the website for comparing their data with others, and for sharing them with HCPs.

HCP, healthcare professional.

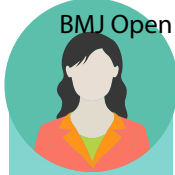
Factors

Outcomes

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For

Initial survey **Initial** **HCP survey and medical record survey**






Special survey **3 months** **Medical record survey**





Symptom survey every 3 months



Follow-up survey **1 year** **Medical record survey**





Follow-up survey **2 years** **Medical record survey**



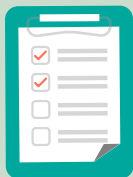


Follow-up survey **3 years** **Medical record survey**





YOURS study



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Database

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b

TRANSFER TO THE WEBSITE



b

PATIENTS CAN REVIEW THEIR OWN DATA



c

PATIENTS CAN COMPARE THEIR DATA WITH OTHERS

PATIENTS CAN SHARE THEIR DATA WITH HCPs



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Ulcerative colitis outcomes research in Japan: protocol for an observational prospective cohort study of YOURS (YOU and Ulcerative colitis: Registry and Social network)

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Study protocol

TITLE

Ulcerative colitis outcomes research in Japan: protocol for an observational prospective cohort study of YOURS (YOu and Ulcerative colitis: Registry and Social network)

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STATISTICAL SUMMARY

Abstract Text	Manuscript Text (Intro - Disc)	References	Figures	Tables
N = 272 (Limit = 300)	N = 1976 (Limit = 4000)	N = 44 (Limit = NA)	N = 3 (Limit = total 5)	N = 2 (Limit = total 5)

ABSTRACT

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease that mainly affects the colon in young patients. Typical symptoms of UC are bloody diarrhea and fecal urgency, which disturb the quality of life (QOL) of patients, and intractable UC leads to hospitalization and colectomy. To improve relevant outcomes such as symptoms, QOL and colectomy, many clinical questions need to be resolved regarding what the ideal lifestyle, psychosocial burden and optimal practice patterns are. In this YOURS study, we will investigate the effect of lifestyle, psychosocial factors and practice patterns on patient-reported outcomes (PRO), hospitalization rate and colectomy rate in Japanese patients with UC.

Methods and analysis

For this prospective cohort study, we recruited 2006 patients from five hospitals (Tokyo and Chiba; May 2018–January 2019). Patients will be able to access their own data and compare them with summarized data from all patients on the website beyond the YOURS study. At baseline, patients will answer a questionnaire regarding lifestyle (diet, exercise, sleep and work), psychosocial factors (stress, depression, social support, etc.) and PRO (symptoms and QOL). Information on practice patterns (eg, medications, endoscopy frequency) will be collected from electronic medical records. Gaps between patients' needs and healthcare professionals' practice will be identified. Follow-up surveys will be conducted periodically for approximately three years. Research questions suggested by patients and healthcare professionals may be used in subsequent surveys. Results from the YOURS study will demonstrate optimal UC management strategies to improve relevant outcomes.

Ethics and dissemination

The study was approved by the ethics committees of five investigational sites before starting the study. The results will be submitted to journals. (UMIN Clinical Trials Registry: UMIN000031995)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The YOURS study is a large-scale, long-term, prospective observational study to explore optimal ulcerative colitis management for improving relevant outcomes.
- The YOURS study reflects the real clinical setting because any concomitant drugs and therapies are allowed.
- The YOURS study can be expanded for subsequent surveys because patients and healthcare professionals can ask research questions not otherwise included in the survey.
- Patients will be able to access their own data and compare them with summarized data from all patients on the website beyond the YOURS study.
- All investigational sites are located within one region of Japan, which may affect the study results, especially because of lifestyle and psychosocial factors.

KEY WORDS

Cohort study; Colitis, ulcerative; Patient outcome assessment; Quality of life.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease with no curative treatment. It mainly affects the colon and is associated with bloody diarrhea and fecal urgency as typical symptoms.[1] Aberrant immunity in the gut is considered to be involved in the pathogenesis of UC,[2] however, the etiology of UC is not fully understood. Ulcerative colitis are increasing around the world, especially in Asia, including Japan.[3-5] The prevalence of UC has been reported to range from 5.3 to 63.6 per 100 000 people in Asia and from 37.5 to 238 per 100 000 people in North America,[1] and differs between regions, with the prevalence in Japan reported as approximately 100 per 100 000 people in 2013.[5]

The onset of UC often has a major influence on patients' quality of life (QOL), and intractable UC can lead to hospitalization and colectomy. Patients need to manage UC throughout their lives with both self-management and support from healthcare professionals (HCPs) to avoid unwanted clinical outcomes, including relapse/exacerbation, hospitalization, and colectomy, as well as to improve patient-reported outcomes such as QOL.

In this YOURS (YOu and Ulcerative colitis: Registry and Social network) study, we identified four main factors/challenges to the improvement of patient outcomes: (1) lifestyle, (2) psychosocial factors, (3) practice patterns and (4) gaps between patients' needs and HCPs' practice (Figure 1).

First, there has been much discussion and debate about the optimal lifestyle (diet, exercise, sleep and work) for UC management. In particular, diet is a critical issue for both patients and their HCPs. Although a large-scale study has reported that the relationship between diet and relapse is of major interest to patients with inflammatory bowel disease (IBD) and their HCPs,[6] only two exploratory studies have examined the relationship.[7, 8] However, the results from these studies were not consistent.

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5 Second, psychosocial factors including stress, depression and social support may affect
6 clinical outcomes in UC. Approximately half of patients with IBD have low QOL and
7 depression,[9] and one third of patients are reported to feel stigmatized.[10] It remains
8 unknown how these psychosocial factors affect disease course.
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15 The third challenge is practice patterns. The Selecting Therapeutic Targets in Inflammatory
16 Bowel Disease (STRIDE) program, published in 2015 by IBD specialists, recommends
17 setting concrete treatment goals as part of a “Treat to Target” strategy.[11] The agreed
18 treatment goals for UC were clinical remission (defined as resolution of rectal bleeding and
19 diarrhea/altered bowel habit) and endoscopic remission (based on endoscopic findings).
20 However, achievement of these treatment goals may be accompanied by decreased QOL
21 due to frequent colonoscopies or side effects caused by immune suppression. Optimal
22 disease monitoring and treatment need to be clarified.
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34 The last challenge is gaps between patients’ needs and HCPs’ practice. A previous survey
35 has identified important differences between patients and HCPs in their perception of the
36 impact of UC symptoms on patients' lives, suggesting that HCPs may underestimate the
37 effect of UC symptoms on patients.[12] However, the effect of perception gaps on patient
38 outcomes is unknown.
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47 The YOURS study is an observational prospective cohort study in patients with UC in Japan
48 that aims to clarify how these four challenges affect relapse/exacerbation, hospitalization,
49 colectomy and patient-reported outcomes such as QOL.
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METHODS AND ANALYSIS

Study design

The YOURS study is an observational prospective cohort study with a 3-year follow-up being conducted at five investigational sites in Japan. Patient registration started in May 2018 and ended in January 2019. As of 11 January, 2019, 2006 patients have been enrolled.

The study is being conducted in compliance with the Declaration of Helsinki, Ethical Guidelines for Medical Research on Humans, Ministry of Education, Culture, Sports, Science and Technology of Japan and Ministry of Health, Labour and Welfare of Japan, and all applicable laws and guidelines. Written informed consent will be obtained from all patients.

The study is registered at the University hospital Medical Information Network (UMIN) Center Clinical Trials Registry (UMIN000031995).

Study population and sample size

Patients diagnosed with UC, as defined by the "Evidence-based Clinical Practice Guidelines for Inflammatory Bowel Disease", [5] who are ≥ 16 years of age at informed consent and are attending the investigational sites are eligible for enrolment.

The sample size was determined by considering the feasibility of enrolling patients.

Outcome measures and survey items

Relapse/exacerbation, hospitalization, colectomy and patient-reported outcomes such as QOL will be assessed as main outcomes. Lifestyle, psychosocial factors, practice patterns and gaps between patients' needs and HCPs' practice will be evaluated as exposures. All surveys will be conducted in Japanese and will include standard, validated questionnaires for most measures of lifestyle, psychosocial factors and symptoms.

At the initial survey, patients will complete written questionnaires with demographic, lifestyle, psychosocial and symptom questions (Table 1, Figure 2). Following the initial survey, patients will complete a three-item brief symptom survey including psychosocial and symptom questions by smartphone application, email, phone or written questionnaire every three months, and a follow-up survey including lifestyle, psychosocial and symptom questions by written questionnaire every year for three years (Table 1, Figure 2). Patients who maintain remission for at least 90 days will complete a special survey by written questionnaire at three months from the time of the initial survey, which includes lifestyle questions focusing on diet, exercise and stress management as strategies to prevent relapse (Table 1, Figure 2). Remission is defined as a stool frequency score of 0 or 1 and a rectal bleeding score of 0 (two-item patient-reported outcome; Table 2).[13] Patients will have the opportunity to provide their own research questions at the initial survey and all follow-up surveys. We plan to categorize and create a ranking of the research questions. The members of the steering committee will review the ranking of these research questions. If the research questions are feasible for this study, they will be included in the subsequent surveys within the YOURS study. The three-item brief symptom survey will provide the most important information for this study because the survey evaluates relapse or exacerbation of UC. In cases where patients are reluctant to complete the follow-up survey, for reasons such as changing hospitals, we will offer to continue with only the brief symptom survey every three months to reduce the number of dropouts.

Table 1. Survey items/questionnaires

	Category	Item (questionnaire)
<i>By patients</i>		
Initial survey	Patient information	Body height, weight, UC history, appendectomy, medical history including malignant tumor, anal fistula and perianal abscess, family history of inflammatory bowel disease, vaccination history, smoking history, education level, economic status and pregnancy history
	Lifestyle	Exercise (IPAQ), sleep (PSQI) and Labor productivity (WPAI)

	Psychosocial factors	Social support (mMOS-SS), medication adherence (ASK-12), comprehensive QOL (QGEN®10 survey), disease-specific QOL (SIBDQ), depression/anxiety (HADS) and stress (JPSS)
	Symptoms	Stool frequency and rectal bleeding (PRO-2), pain (NRS) and fatigue (FACIT-F)
	Others	Research questions not included in this survey
Special survey (in patients in remission for at least 90 days, at 3 months from the time of initial survey)	Lifestyle	Diet (BDHQ)
	Others	Diet, exercise and stress management strategies to prevent relapse
Symptom survey (every 3 months)	Psychosocial factors	Disease-specific QOL (QDIS®-1)
	Symptoms	Stool frequency and rectal bleeding (PRO-2)
Follow-up survey (every year)	Lifestyle	Sleep (PSQI) and Labor productivity (WPAI)
	Psychosocial factors	Medication adherence (ASK-12), comprehensive QOL (QGEN®10 survey), disease-specific QOL (SIBDQ), depression/anxiety (HADS) and stress (JPSS)
	Symptoms	Stool frequency and rectal bleeding (PRO-2), pain (NRS) and fatigue (FACIT-F)
	Others	Research questions not included in this survey
By HCP		
HCP survey (initial)	-	Observations related to lifestyle guidance for diet, exercise and strategies to avoid stress; research questions not included in this survey
Medical record survey (initial only)	Patient information	Age, sex, worst disease extent (eg, pancolitis, left-sided colitis, extensive colitis), extra-intestinal complications and treatment history
Medical record survey (initial, 3 months from the initial survey, every year)	Medical information	Partial Mayo score, medication, observation of endoscope and pathologic observation, <i>Clostridium difficile</i> infection, blood exam, calprotectin in stool, hospitalization, colectomy, pregnancy, adverse events and malignancy

Abbreviations: ASK-12,[14-17] Adherence Starts with Knowledge-12; BDHQ,[18, 19] Brief-type self-administered Diet History Questionnaire; FACIT-F,[20-22] Functional Assessment of Chronic Illness Therapy - Fatigue; HADS,[23-26] Hospital Anxiety and Depression Scale; HCP, healthcare professional; IPAQ,[27, 28] International Physical Activities Questionnaire; JPSS,[29, 30] Japanese version of the Perceived Stress Scale; mMOS-SS,[31-33] modified Medical Outcomes Study Social Support Survey; NRS,[34] Numerical Rating Scale; PRO-2,[13] two-item patient-reported outcomes; PSQI,[35, 36] Pittsburgh Sleep Quality Index;

QDIS[®],[37] Quality of life Disease-specific Impact Scale; QGEN[®],[38] Quality of life GENERAL; QOL, quality of life; SIBDQ,[39-41] Short version of Inflammatory Bowel Disease Questionnaire; UC, ulcerative colitis; WPAI,[42, 43] Work Productivity and Activity Impairment questionnaire.

Table 2. Definition of stool frequency score and rectal bleeding score in PRO-2

Score	Definition
<i>Stool frequency</i>	
0	Normal number of stools
1	1-2 stools more than normal
2	3-4 stools more than normal
3	5 or more stools more than normal
<i>Rectal bleeding</i>	
0	None
1	Streaks of blood with stool less than half the time
2	Obvious blood with stool most of the time
3	Blood alone passed

Abbreviation: PRO-2, two-item patient-reported outcomes.

In the HCP survey, HCPs will complete written questionnaires about their guidance to patients with remission regarding diet, exercise and stress management in order to prevent relapse. Answers from patients and HCPs will be compared and any gaps in the perception of the ideal lifestyle to prevent relapses will be identified and explored. In addition, HCPs will collect patients' medical information such as medication use, blood exams, stool exams, endoscopic findings, pathologic findings, hospitalizations, colectomy status and adverse events (throughout the study) from electronic medical records at all surveys (Table 1, Figure 2).

Data management

The YOURS study uses an electronic data capture (EDC) system to register patients, collect survey answers and create a database, which can be accessed securely by only those investigators who have received appropriate training. The principal investigators are responsible for ensuring data quality.

Feedback to patients

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3 Patients will be provided written feedback on their data compared with the other patients
4 participating in the YOURS study. Moreover, patients can use the website for reviewing their
5 data over time, comparing with others, and sharing their data with HCPs via the website,
6 provided the patients have requested access and agreed to the transfer of their data from the
7 database to the website with written informed consent (Figure 3).
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13 14 15 **Statistical analysis**

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17 Analysis groups will be determined for each outcome measure and survey item. The baseline
18 data on demographics, lifestyle, psychosocial factors, practice patterns, and gaps between
19 patients' needs and HCPs' practice will be summarized. The following statistical analyses to
20 clarify the association of these baseline data with relapse/exacerbation, hospitalization,
21 colectomy, and patient-reported outcomes such as QOL will be conducted.
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31 Logistic regression analysis or Cox proportional hazard model will be used for analysis of
32 binary variables. Linear regression analysis will be used for analysis of continuous variables.
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34 Multilevel analysis may be used for considering differences between investigational sites.
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36 Confounding factors will be adjusted appropriately for all analyses.
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42 Interim database locks and interim analyses are planned as follows: initial survey, special
43 survey at three months from the time of the initial survey, and follow-up surveys at two and
44 three years after the initial survey.
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49 **Patient and public involvement statement**

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51 We will collect research questions from both patients and HCPs from surveys in the YOURS
52 study. If the research questions are feasible for this study, they will be included in the
53 subsequent surveys within the YOURS study.
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ETHICS AND DISSEMINATION

The YOURS study is sponsored by Takeda Pharmaceutical Company Limited (Tokyo, Japan) and advice on the study plan was obtained from the Japanese Society for Inflammatory Bowel Disease. The study is managed by six joint research organizations, including Takeda and five investigational sites: Tokyo Medical and Dental University, Medical Hospital (Tokyo, Japan); Kitasato University Kitasato Institute Hospital (Tokyo, Japan); Kyorin University Hospital (Tokyo, Japan); Tokyo Women's Medical University Hospital (Tokyo, Japan); and Toho University Sakura Medical Center (Chiba, Japan), and was approved by the ethics committees of five investigational sites before starting the study. The YOURS study has a steering committee consisting of medical experts conducting the study, representatives of the joint research organizations and clinical epidemiology experts. The roles of the steering committee are to supervise the overall study operation, provide medical expertise guidance, ensure the scientific quality of the study is at a high level and update the protocol appropriately when needed. The results will be submitted to journals for publication.

DISCUSSION

There are four primary goals of the YOURS study: (1) develop a platform to share clinical knowledge and patient experience, (2) define optimal care for UC, (3) fill gaps between patients' needs and HCPs' practice, and (4) improve relevant outcomes. To achieve these goals, the YOURS study will investigate how four main challenges (lifestyle, psychosocial factors, practice patterns and gaps between patients' needs and HCPs' practice) affect relapse/exacerbation, hospitalization, colectomy and patient-reported outcomes such as QOL.

Using the YOURS study results, we plan to create a booklet to clarify how challenges such as lifestyle, psychosocial factors, practice patterns and gaps between patients' needs and HCPs' practice affect clinical outcomes. Although booklets are a preferred adjunct source of information for patients with IBD and it is important to distribute booklets, the same information will also be disseminated in other ways, such as websites, as needed.[44] The YOURS study booklet will include specific information on diet, exercise, sleep, work, stress, depression and social support. Moreover, if we identify any gaps between patients' needs and HCPs' practice regarding lifestyle guidance, we will include that information in the booklet as background information. We anticipate that the booklet will facilitate the sharing of information between patients and HCPs, thereby helping to bridge gaps between patients' needs and HCPs' practice.

The YOURS study is a large-scale, long-term, prospective observational study without any prohibited concomitant drugs and therapies, thereby reflecting real clinical settings. However, as all investigational sites are located in Tokyo or Chiba (which is near Tokyo) in Japan, the applicability of the study results to other locations may be affected by lifestyle and psychosocial factors influenced by regional, country, and/or cultural differences. The other limitation of this study is the possibility that patients will confuse some of the questions, because various kinds of scales are used in each survey to evaluate lifestyle and

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3 psychosocial factors. The YOURS study can potentially be expanded in subsequent surveys
4 within the study because patients and HCPs can ask research questions not otherwise
5 included in the survey.
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11 In conclusion, the YOURS study provides an important opportunity to clarify how challenges
12 such as lifestyle, psychosocial factors, practice patterns and gaps between patients' needs
13 and HCPs' practice affect clinical outcomes in patients with UC in Japan. We anticipate that
14 results from the YOURS study will demonstrate optimal UC management strategies to
15 improve relevant outcomes.
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Authors' contributions

All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. H Yamazaki, K Matsuoka, J Fernandez and S Fukuhara were involved in the study design. K Matsuoka, T Hibi, M Watanabe and T Hisamatsu are investigators and have collected the data in the study.

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Disclaimer

Takeda Pharmaceutical Company Limited has been or will be involved in the study design, data collection, data analysis, and preparation of the manuscript.

Competing interests

H Yamazaki has no conflicts of interest to declare. K Matsuoka has received grants and personal fees from Sekisui Medical, AbbVie, and ThermoFisher Scientific, grants from Alfresa Pharma Corporation, personal fees from Mitsubishi-Tanabe Pharma, Eisai, Kyorin

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3 Pharmaceutical, Asahi Kasei Medical, Mochida Pharmaceutical, Kissei, Kyowa Hakko Kirin,
4 Takeda Pharmaceutical, Covidien, Janssen Pharmaceutical, Pfizer, EA Pharma, Astellas,
5 Zeria Pharmaceutical, Celltrion and JIMRO. J Fernandez is an employee of Takeda
6 Pharmaceutical Company Limited and owns restricted stocks of Takeda Pharmaceutical
7 Company Limited and GlaxoSmithKline. T Hibi has received grants and personal fees from
8 AbbVie GK, JIMRO Co., Ltd, EA Pharma and Zeria Pharmaceutical, grants from Otsuka
9 Pharmaceutical Co., Ltd, personal fees from Mitsubishi-Tanabe Pharm, Kyorin
10 Pharmaceutical, Janssen, Mochida Pharmaceutical, Takeda Pharmaceutical, Gilead
11 Sciences, Celltrion, Nippon Kayaku, Kissei Pharmaceutical, Miyarisan Pharmaceutical,
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13 Watanabe has received grants and personal fees from Ajinomoto Pharma Co., Ltd, Kyorin
14 Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Co., Ltd, Takeda Pharmaceutical Co.,
15 Ltd, Eisai Co., Ltd, Otsuka Pharma Co., Ltd, Kyowa Hakko Kirin Co., Ltd, Zeria
16 Pharmaceutical Co., Ltd, JIMRO Co., Ltd, Asahi Kasei Kuraray Medical Co., Ltd, EA Pharma
17 Co., Ltd, AbbVie GK, Astellas Pharma Inc., Daiichi Sankyo Co., Ltd, Chugai Pharmaceutical
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30 Pfizer Japan Inc. and MSD K.K..

Patient consent

Obtained.

Ethics approval

The study was approved by the ethics committees of five investigational sites.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data sharing statement

As enrolment has only recently finished and no analysis has been conducted yet, there are no data that can be shared at this time.

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FIGURE LEGENDS

Figure 1. Factors and outcomes assessed in the YOURS study.

All four factors can contribute to all four outcomes.

HCP, healthcare professional.

Figure 2. Study design.

Surveys on the left side are for patients, and surveys on the right side are for HCPs.

All surveys were completed by written questionnaires, except for the symptom survey, which could be completed by smartphone application, email, phone, or written questionnaire. The special survey at 3 months from the time of initial survey was only completed by patients who maintained remission for at least 90 days.

HCP, healthcare professional.

Figure 3. Feedback scheme of the YOURS study

- a) Survey answers and medical records will be collected from patients and HCPs by written questionnaire, smartphone application, email, or phone, and stored in the YOURS study database.
- b) Patients can use a website for reviewing their own data over time if the patients have requested access and agreed to the transfer of their data to the website.
- c) Patients can also use the website for comparing their data with others, and for sharing their data with HCPs via the website.

HCP, healthcare professional.

Outcomes

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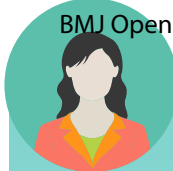
Factors

- 1 ●
- 2 ① Lifestyle
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- 5 ② Psychosocial burden
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- 8 ③ Practice patterns
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- 11 ④ Gaps between patients' needs and HCPs' practice
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- 1 ●
- 2 ① Relapse/exacerbation
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- 5 ② Hospitalization
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- 8 ③ Colectomy
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- 11 ④ Patient-reported outcomes
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For peer review only - <http://bmjopen.bmj.com/site/about/guidelines.xhtml>



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For

Initial survey **Initial** **HCP survey and medical record survey**

Special survey **3 months** **Medical record survey**

Symptom survey every 3 months

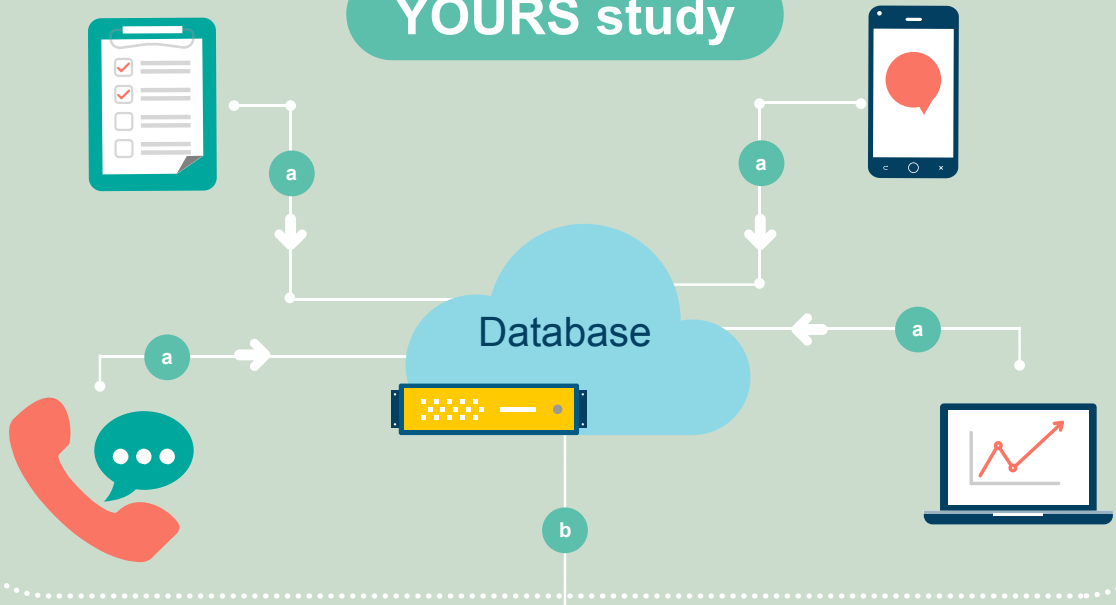


Follow-up survey **1 year** **Medical record survey**

Follow-up survey **2 years** **Medical record survey**

Follow-up survey **3 years** **Medical record survey**

YOURS study

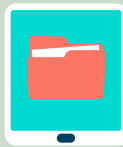


TRANSFER TO THE WEBSITE



b

PATIENTS CAN REVIEW THEIR OWN DATA



c

PATIENTS CAN COMPARE THEIR DATA WITH OTHERS

PATIENTS CAN SHARE THEIR DATA WITH HCPs



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Ulcerative colitis outcomes research in Japan: protocol for an observational prospective cohort study of YOURS (YOU and Ulcerative colitis: Registry and Social network)

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TITLE

Ulcerative colitis outcomes research in Japan: protocol for an observational prospective cohort study of YOURS (YOu and Ulcerative colitis: Registry and Social network)

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ABSTRACT

Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease that mainly affects the colon in young patients. Typical symptoms of UC are bloody diarrhea and fecal urgency, which disturb the quality of life (QOL) of patients, and intractable UC leads to hospitalization and colectomy. To improve relevant outcomes such as symptoms, QOL and colectomy, many clinical questions need to be resolved regarding what the ideal lifestyle, psychosocial burden and optimal practice patterns are. In this YOURS study, we will investigate the effect of lifestyle, psychosocial factors and practice patterns on patient-reported outcomes (PRO), hospitalization rate and colectomy rate in Japanese patients with UC.

Methods and analysis

For this prospective cohort study, we recruited 2006 patients from five hospitals (Tokyo and Chiba; May 2018–January 2019). Patients will be able to access their own data and compare them with summarized data from all patients on the website beyond the YOURS study. At baseline, patients will answer a questionnaire regarding lifestyle (diet, exercise, sleep and work), psychosocial factors (stress, depression, social support, etc.) and PRO (symptoms and QOL). Information on practice patterns (eg, medications, endoscopy frequency) will be collected from electronic medical records. Gaps between patients' needs and healthcare professionals' practice will be identified. Follow-up surveys will be conducted periodically for approximately three years. Research questions suggested by patients and healthcare professionals may be used in subsequent surveys. Results from the YOURS study will demonstrate optimal UC management strategies to improve relevant outcomes.

Ethics and dissemination

The study was approved by the ethics committees of five investigational sites before starting the study. The results will be submitted to journals. (UMIN Clinical Trials Registry: UMIN000031995)

STRENGTHS AND LIMITATIONS OF THIS STUDY

- The YOURS study is a large-scale, long-term, prospective observational study to explore optimal ulcerative colitis management for improving relevant outcomes.
- The YOURS study reflects the real clinical setting because any concomitant drugs and therapies are allowed.
- The YOURS study can be expanded for subsequent surveys because patients and healthcare professionals can ask research questions not otherwise included in the survey.
- Patients will be able to access their own data and compare them with summarized data from all patients on the website beyond the YOURS study.
- All investigational sites are located within one region of Japan, which may affect the study results, especially because of lifestyle and psychosocial factors.

KEY WORDS

Cohort study; Colitis, ulcerative; Patient outcome assessment; Quality of life.

INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease with no curative treatment. It mainly affects the colon and is associated with bloody diarrhea and fecal urgency as typical symptoms.[1] Aberrant immunity in the gut is considered to be involved in the pathogenesis of UC,[2] however, the etiology of UC is not fully understood. Ulcerative colitis are increasing around the world, especially in Asia, including Japan.[3-5] The prevalence of UC has been reported to range from 5.3 to 63.6 per 100 000 people in Asia and from 37.5 to 238 per 100 000 people in North America,[1] and differs between regions, with the prevalence in Japan reported as approximately 100 per 100 000 people in 2013.[5]

The onset of UC often has a major influence on patients' quality of life (QOL), and intractable UC can lead to hospitalization and colectomy. Patients need to manage UC throughout their lives with both self-management and support from healthcare professionals (HCPs) to avoid unwanted clinical outcomes, including relapse/exacerbation, hospitalization, and colectomy, as well as to improve patient-reported outcomes such as QOL.

In this YOURS (YOu and Ulcerative colitis: Registry and Social network) study, we identified four main factors/challenges to the improvement of patient outcomes: (1) lifestyle, (2) psychosocial factors, (3) practice patterns and (4) gaps between patients' needs and HCPs' practice (Figure 1).

First, there has been much discussion and debate about the optimal lifestyle (diet, exercise, sleep and work) for UC management. In particular, diet is a critical issue for both patients and their HCPs. Although a large-scale study has reported that the relationship between diet and relapse is of major interest to patients with inflammatory bowel disease (IBD) and their HCPs,[6] only two exploratory studies have examined the relationship.[7, 8] However, the results from these studies were not consistent.

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5 Second, psychosocial factors including stress, depression and social support may affect
6 clinical outcomes in UC. Approximately half of patients with IBD have low QOL and
7 depression,[9] and one third of patients are reported to feel stigmatized.[10] It remains
8 unknown how these psychosocial factors affect disease course.
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16 The third challenge is practice patterns. The Selecting Therapeutic Targets in Inflammatory
17 Bowel Disease (STRIDE) program, published in 2015 by IBD specialists, recommends
18 setting concrete treatment goals as part of a “Treat to Target” strategy.[11] The agreed
19 treatment goals for UC were clinical remission (defined as resolution of rectal bleeding and
20 diarrhea/altered bowel habit) and endoscopic remission (based on endoscopic findings).
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22 However, achievement of these treatment goals may be accompanied by decreased QOL
23 due to frequent colonoscopies or side effects caused by immune suppression. Optimal
24 disease monitoring and treatment need to be clarified.
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35 The last challenge is gaps between patients’ needs and HCPs’ practice. A previous survey
36 has identified important differences between patients and HCPs in their perception of the
37 impact of UC symptoms on patients' lives, suggesting that HCPs may underestimate the
38 effect of UC symptoms on patients.[12] However, the effect of perception gaps on patient
39 outcomes is unknown.
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48 The YOURS study is an observational prospective cohort study in patients with UC in Japan
49 that aims to clarify how these four challenges affect relapse/exacerbation, hospitalization,
50 colectomy and patient-reported outcomes such as QOL.
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METHODS AND ANALYSIS

Study design

The YOURS study is an observational prospective cohort study with a 3-year follow-up being conducted at five investigational sites in Japan. Patient registration started in May 2018 and ended in January 2019. As of 11 January, 2019, 2006 patients have been enrolled.

The study is being conducted in compliance with the Declaration of Helsinki, Ethical Guidelines for Medical Research on Humans, Ministry of Education, Culture, Sports, Science and Technology of Japan and Ministry of Health, Labour and Welfare of Japan, and all applicable laws and guidelines. Written informed consent will be obtained from all patients.

The study is registered at the University hospital Medical Information Network (UMIN) Center Clinical Trials Registry (UMIN000031995).

Study population and sample size

Patients diagnosed with UC, as defined by the "Evidence-based Clinical Practice Guidelines for Inflammatory Bowel Disease",^[5] who are ≥ 16 years of age at informed consent and are attending the investigational sites are eligible for enrolment.

The sample size was determined by considering the feasibility of enrolling patients.

Outcome measures and survey items

Relapse/exacerbation, hospitalization, colectomy and patient-reported outcomes such as QOL will be assessed as main outcomes. Lifestyle, psychosocial factors, practice patterns and gaps between patients' needs and HCPs' practice will be evaluated as exposures. All surveys will be conducted in Japanese and will include standard, validated questionnaires for most measures of lifestyle, psychosocial factors and symptoms.

At the initial survey, patients will complete written questionnaires with demographic, lifestyle, psychosocial and symptom questions (Table 1, Figure 2). Following the initial survey, patients will complete a three-item brief symptom survey including psychosocial and symptom questions by smartphone application, email, phone or written questionnaire every three months, and a follow-up survey including lifestyle, psychosocial and symptom questions by written questionnaire every year for three years (Table 1, Figure 2). Patients who maintain remission for at least 90 days will complete a special survey by written questionnaire at three months from the time of the initial survey, which includes lifestyle questions focusing on diet, exercise and stress management as strategies to prevent relapse (Table 1, Figure 2). Remission is defined as a stool frequency score of 0 or 1 and a rectal bleeding score of 0 (two-item patient-reported outcome; Table 2).[13] Patients will have the opportunity to provide their own research questions at the initial survey and all follow-up surveys. We plan to categorize and create a ranking of the research questions. The members of the steering committee will review the ranking of these research questions. If the research questions are feasible for this study, they will be included in the subsequent surveys within the YOURS study. The three-item brief symptom survey will provide the most important information for this study because the survey evaluates relapse or exacerbation of UC. In cases where patients are reluctant to complete the follow-up survey, for reasons such as changing hospitals, we will offer to continue with only the brief symptom survey every three months to reduce the number of dropouts.

Table 1. Survey items/questionnaires

	Category	Item (questionnaire)
<i>By patients</i>		
Initial survey	Patient information	Body height, weight, UC history, appendectomy, medical history including malignant tumor, anal fistula and perianal abscess, family history of inflammatory bowel disease, vaccination history, smoking history, education level, economic status and pregnancy history
	Lifestyle	Exercise (IPAQ), sleep (PSQI) and Labor productivity (WPAI)

	Psychosocial factors	Social support (mMOS-SS), medication adherence (ASK-12), comprehensive QOL (QGEN®10 survey), disease-specific QOL (SIBDQ), depression/anxiety (HADS) and stress (JPSS)
	Symptoms	Stool frequency and rectal bleeding (PRO-2), pain (NRS) and fatigue (FACIT-F)
	Others	Research questions not included in this survey
Special survey (in patients in remission for at least 90 days, at 3 months from the time of initial survey)	Lifestyle	Diet (BDHQ)
	Others	Diet, exercise and stress management strategies to prevent relapse
Symptom survey (every 3 months)	Psychosocial factors	Disease-specific QOL (QDIS®-1)
	Symptoms	Stool frequency and rectal bleeding (PRO-2)
Follow-up survey (every year)	Lifestyle	Sleep (PSQI) and Labor productivity (WPAI)
	Psychosocial factors	Medication adherence (ASK-12), comprehensive QOL (QGEN®10 survey), disease-specific QOL (SIBDQ), depression/anxiety (HADS) and stress (JPSS)
	Symptoms	Stool frequency and rectal bleeding (PRO-2), pain (NRS) and fatigue (FACIT-F)
	Others	Research questions not included in this survey
By HCP		
HCP survey (initial)	-	Observations related to lifestyle guidance for diet, exercise and strategies to avoid stress; research questions not included in this survey
Medical record survey (initial only)	Patient information	Age, sex, worst disease extent (eg, pancolitis, left-sided colitis, extensive colitis), extra-intestinal complications and treatment history
Medical record survey (initial, 3 months from the initial survey, every year)	Medical information	Partial Mayo score, medication, observation of endoscope and pathologic observation, <i>Clostridium difficile</i> infection, blood exam, calprotectin in stool, hospitalization, colectomy, pregnancy, adverse events and malignancy

Abbreviations: ASK-12,[14-17] Adherence Starts with Knowledge-12; BDHQ,[18, 19] Brief-type self-administered Diet History Questionnaire; FACIT-F,[20-22] Functional Assessment of Chronic Illness Therapy - Fatigue; HADS,[23-26] Hospital Anxiety and Depression Scale; HCP, healthcare professional; IPAQ,[27, 28] International Physical Activities Questionnaire; JPSS,[29, 30] Japanese version of the Perceived Stress Scale; mMOS-SS,[31-33] modified Medical Outcomes Study Social Support Survey; NRS,[34] Numerical Rating Scale; PRO-2,[13] two-item patient-reported outcomes; PSQI,[35, 36] Pittsburgh Sleep Quality Index;

QDIS[®],[37] Quality of life Disease-specific Impact Scale; QGEN[®],[38] Quality of life GENERAL; QOL, quality of life; SIBDQ,[39-41] Short version of Inflammatory Bowel Disease Questionnaire; UC, ulcerative colitis; WPAI,[42, 43] Work Productivity and Activity Impairment questionnaire.

Table 2. Definition of stool frequency score and rectal bleeding score in PRO-2

Score	Definition
<i>Stool frequency</i>	
0	Normal number of stools
1	1-2 stools more than normal
2	3-4 stools more than normal
3	5 or more stools more than normal
<i>Rectal bleeding</i>	
0	None
1	Streaks of blood with stool less than half the time
2	Obvious blood with stool most of the time
3	Blood alone passed

Abbreviation: PRO-2, two-item patient-reported outcomes.

In the HCP survey, HCPs will complete written questionnaires about their guidance to patients with remission regarding diet, exercise and stress management in order to prevent relapse. Answers from patients and HCPs will be compared and any gaps in the perception of the ideal lifestyle to prevent relapses will be identified and explored. In addition, HCPs will collect patients' medical information such as medication use, blood exams, stool exams, endoscopic findings, pathologic findings, hospitalizations, colectomy status and adverse events (throughout the study) from electronic medical records at all surveys (Table 1, Figure 2).

Data management

The YOURS study uses an electronic data capture (EDC) system to register patients, collect survey answers and create a database, which can be accessed securely by only those investigators who have received appropriate training. The principal investigators are responsible for ensuring data quality.

Feedback to patients

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3 Patients will be provided written feedback on their data compared with the other patients
4 participating in the YOURS study. Moreover, patients can use the website for reviewing their
5 data over time, comparing with others, and sharing their data with HCPs via the website,
6 provided the patients have requested access and agreed to the transfer of their data from the
7 database to the website with written informed consent (Figure 3).
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13 14 15 **Statistical analysis**

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17 Analysis groups will be determined for each outcome measure and survey item. The baseline
18 data on demographics, lifestyle, psychosocial factors, practice patterns, and gaps between
19 patients' needs and HCPs' practice will be summarized. The following statistical analyses to
20 clarify the association of these baseline data with relapse/exacerbation, hospitalization,
21 colectomy, and patient-reported outcomes such as QOL will be conducted.
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31 Logistic regression analysis or Cox proportional hazard model will be used for analysis of
32 binary variables. Linear regression analysis will be used for analysis of continuous variables.
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34 Multilevel analysis may be used for considering differences between investigational sites.
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36 Confounding factors will be adjusted appropriately for all analyses.
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42 Interim database locks and interim analyses are planned as follows: initial survey, special
43 survey at three months from the time of the initial survey, and follow-up surveys at two and
44 three years after the initial survey.
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49 **Patient and public involvement statement**

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51 We will collect research questions from both patients and HCPs from surveys in the YOURS
52 study. If the research questions are feasible for this study, they will be included in the
53 subsequent surveys within the YOURS study.
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ETHICS AND DISSEMINATION

The YOURS study is sponsored by Takeda Pharmaceutical Company Limited (Tokyo, Japan) and advice on the study plan was obtained from the Japanese Society for Inflammatory Bowel Disease. The study is managed by six joint research organizations, including Takeda and five investigational sites: Tokyo Medical and Dental University, Medical Hospital (Tokyo, Japan); Kitasato University Kitasato Institute Hospital (Tokyo, Japan); Kyorin University Hospital (Tokyo, Japan); Tokyo Women's Medical University Hospital (Tokyo, Japan); and Toho University Sakura Medical Center (Chiba, Japan), and was approved by the ethics committees of five investigational sites before starting the study. The YOURS study has a steering committee consisting of medical experts conducting the study, representatives of the joint research organizations and clinical epidemiology experts. The roles of the steering committee are to supervise the overall study operation, provide medical expertise guidance, ensure the scientific quality of the study is at a high level and update the protocol appropriately when needed. The results will be submitted to journals for publication.

DISCUSSION

There are four primary goals of the YOURS study: (1) develop a platform to share clinical knowledge and patient experience, (2) define optimal care for UC, (3) fill gaps between patients' needs and HCPs' practice, and (4) improve relevant outcomes. To achieve these goals, the YOURS study will investigate how four main challenges (lifestyle, psychosocial factors, practice patterns and gaps between patients' needs and HCPs' practice) affect relapse/exacerbation, hospitalization, colectomy and patient-reported outcomes such as QOL.

Using the YOURS study results, we plan to create a booklet to clarify how challenges such as lifestyle, psychosocial factors, practice patterns and gaps between patients' needs and HCPs' practice affect clinical outcomes. Although booklets are a preferred adjunct source of information for patients with IBD and it is important to distribute booklets, the same information will also be disseminated in other ways, such as websites, as needed.[44] The YOURS study booklet will include specific information on diet, exercise, sleep, work, stress, depression and social support. Moreover, if we identify any gaps between patients' needs and HCPs' practice regarding lifestyle guidance, we will include that information in the booklet as background information. We anticipate that the booklet will facilitate the sharing of information between patients and HCPs, thereby helping to bridge gaps between patients' needs and HCPs' practice.

The YOURS study is a large-scale, long-term, prospective observational study without any prohibited concomitant drugs and therapies, thereby reflecting real clinical settings. However, as all investigational sites are located in Tokyo or Chiba (which is near Tokyo) in Japan, the applicability of the study results to other locations may be affected by lifestyle and psychosocial factors influenced by regional, country, and/or cultural differences. The other limitation of this study is the possibility that patients will confuse some of the questions, because various kinds of scales are used in each survey to evaluate lifestyle and

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3 psychosocial factors. The YOURS study can potentially be expanded in subsequent surveys
4 within the study because patients and HCPs can ask research questions not otherwise
5 included in the survey.
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11 In conclusion, the YOURS study provides an important opportunity to clarify how challenges
12 such as lifestyle, psychosocial factors, practice patterns and gaps between patients' needs
13 and HCPs' practice affect clinical outcomes in patients with UC in Japan. We anticipate that
14 results from the YOURS study will demonstrate optimal UC management strategies to
15 improve relevant outcomes.
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Authors' contributions

All authors participated in the interpretation of study results, and in the drafting, critical revision, and approval of the final version of the manuscript. H Yamazaki, K Matsuoka, J Fernandez and S Fukuhara were involved in the study design. K Matsuoka, T Hibi, M Watanabe and T Hisamatsu are investigators and have collected the data in the study.

Funding statement

Clinical experts, clinical epidemiologists, and Takeda Pharmaceutical Company Limited (Takeda) discussed and developed the protocol, and Takeda contracted out the collection of supporting data by clinicians to site management organizations. Takeda will also contract out data analysis to a third organization. Regarding manuscript preparation, Jovelle Fernandez, an employee of Takeda Japan Medical Office, is one of the authors of this manuscript. She participated in the study design, interpretation of study results, drafting, critical revision, and approval of the final version of the manuscript, as stated in the Authors' contributions section. Takeda contracted out medical writing to Yukiko Homma, MPharm and Rebecca Lew, PhD, CMPP of ProScribe – Envision Pharma Group. ProScribe's services complied with international guidelines for Good Publication Practice (GPP3).

Disclaimer

Takeda Pharmaceutical Company Limited has been or will be involved in the study design, data collection, data analysis, and preparation of the manuscript.

Competing interests

H Yamazaki has no conflicts of interest to declare. K Matsuoka has received grants and personal fees from Sekisui Medical, AbbVie, and Thermofisher Scientific, grants from Alfresa Pharma Corporation, personal fees from Mitsubishi-Tanabe Pharma, Eisai, Kyorin Pharmaceutical, Asahi Kasei Medical, Mochida Pharmaceutical, Kissei, Kyowa Hakko Kirin, Takeda Pharmaceutical, Covidien, Janssen Pharmaceutical, Pfizer, EA Pharma, Astellas, Zeria Pharmaceutical, Celltrion and JIMRO. J Fernandez is an employee of Takeda Pharmaceutical Company Limited and owns restricted stocks of Takeda Pharmaceutical Company Limited and GlaxoSmithKline. T Hibi has received grants and personal fees from AbbVie GK, JIMRO Co., Ltd, EA Pharma and Zeria Pharmaceutical, grants from Otsuka Pharmaceutical Co., Ltd, personal fees from Mitsubishi-Tanabe Pharm, Kyorin Pharmaceutical, Janssen, Mochida Pharmaceutical, Takeda Pharmaceutical, Gilead Sciences, Celltrion, Nippon Kayaku, Kissei Pharmaceutical, Miyarisan Pharmaceutical, Ferring Pharmaceutical, Eli Lilly, Pfizer Japan Inc. and Nichi-Iko Pharmaceutical. M Watanabe has received grants and personal fees from Ajinomoto Pharma Co., Ltd, Kyorin Pharmaceutical Co., Ltd, Mitsubishi Tanabe Pharma Co., Ltd, Takeda Pharmaceutical Co., Ltd, Eisai Co., Ltd, Otsuka Pharma Co., Ltd, Kyowa Hakko Kirin Co., Ltd, Zeria Pharmaceutical Co., Ltd, JIMRO Co., Ltd, Asahi Kasei Kuraray Medical Co., Ltd, EA Pharma Co., Ltd, AbbVie GK, Astellas Pharma Inc., Daiichi Sankyo Co., Ltd, Chugai Pharmaceutical Co., Ltd, Gilead Sciences, Nippon Kayaku Co., Ltd., Mochida Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., Celltrion Healthcare Co., Ltd, Pfizer Japan Inc. and Miyarisan Pharmaceutical Co., Ltd.; grants from Toray Industries, MSD K.K., Bristol-Myers K.K., Taiho Pharmaceutical Co., Ltd., Ayumi Pharmaceutical Co., Ltd. and Shionogi & Co., Ltd.; and personal fees from Kissei Pharmaceutical Co., Ltd., Nichi-Iko Pharmaceutical Co., Ltd., Celgene and Novartis. T Hisamatsu has received grants and personal fees from Mitsubishi Tanabe Pharma, EA Pharma, AbbVie GK, JIMRO, Zeria, Kyorin Pharmaceutical, Takeda Pharmaceutical, Pfizer Japan and Mochida Pharmaceutical; grants from Asahi Kasei Kuraray

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4
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6
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9 Kirin Co., Ltd, Daiichi Sankyo Co., Ltd, Bayer Yakuhin, Ltd, Otsuka Pharmaceutical Co., Ltd,
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11 Pfizer Japan Inc. and MSD K.K..
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15 **Patient consent**

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17 Obtained.
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22 **Ethics approval**

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24 The study was approved by the ethics committees of five investigational sites.
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28 **Provenance and peer review**

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30 Not commissioned; externally peer reviewed.
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35 **Data sharing statement**

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37 As enrolment has only recently finished and no analysis has been conducted yet, there are
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39 no data that can be shared at this time.
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43 **Open access**

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53 See: <http://creativecommons.org/licenses/by-nc/4.0/>.
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FIGURE LEGENDS

Figure 1. Factors and outcomes assessed in the YOURS study.

All four factors can contribute to all four outcomes.

HCP, healthcare professional.

Figure 2. Study design.

Surveys on the left side are for patients, and surveys on the right side are for HCPs.

All surveys were completed by written questionnaires, except for the symptom survey, which could be completed by smartphone application, email, phone, or written questionnaire. The special survey at 3 months from the time of initial survey was only completed by patients who maintained remission for at least 90 days.

HCP, healthcare professional.

Figure 3. Feedback scheme of the YOURS study

- a) Survey answers and medical records will be collected from patients and HCPs by written questionnaire, smartphone application, email, or phone, and stored in the YOURS study database.
- b) Patients can use a website for reviewing their own data over time if the patients have requested access and agreed to the transfer of their data to the website.
- c) Patients can also use the website for comparing their data with others, and for sharing their data with HCPs via the website.

HCP, healthcare professional.

Outcomes

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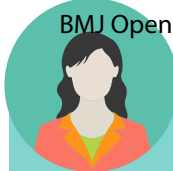
Factors

- 1 ●
- 2 ① Lifestyle
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- 5 ② Psychosocial burden
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- 8 ③ Practice patterns
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- 11 ④ Gaps between patients' needs and HCPs' practice
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- 1 ●
- 2 ① Relapse/exacerbation
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- 5 ② Hospitalization
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- 8 ③ Colectomy
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- 11 ④ Patient-reported outcomes
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For

Initial survey **Initial** **HCP survey and medical record survey**

Special survey **3 months** **Medical record survey**

Symptom survey every 3 months

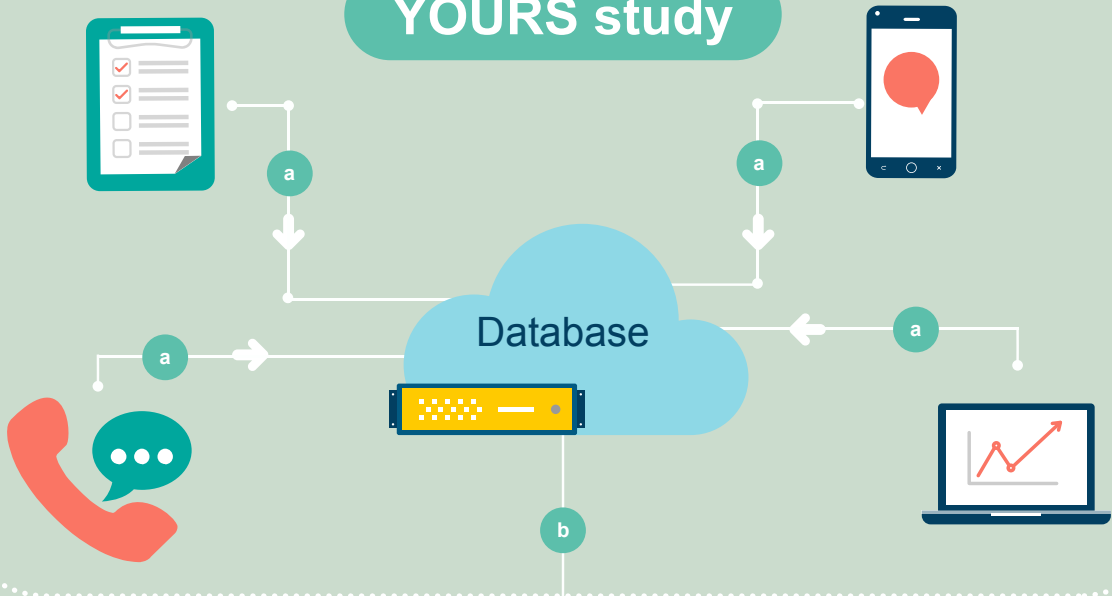


Follow-up survey **1 year** **Medical record survey**

Follow-up survey **2 years** **Medical record survey**

Follow-up survey **3 years** **Medical record survey**

YOURS study

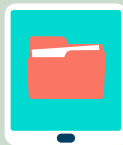


TRANSFER TO THE WEBSITE



b

PATIENTS CAN REVIEW THEIR OWN DATA



c

PATIENTS CAN COMPARE THEIR DATA WITH OTHERS

PATIENTS CAN SHARE THEIR DATA WITH HCPs



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