A COMPARISON OF DISEASE ACTIVITY, QUALITY OF LIFE AND COSTS FOLLOWING IMPLEMENTATION OF A DIGITAL MONITORING STRATEGY USING CROHN’S COLITIS CARE (CCCARE) VERSUS STANDARD OF CARE AMONG PEOPLE WITH INFLAMMATORY BOWEL DISEASE (IBD) FROM A REMOTE AND RURAL LOCATION

**SPONSOR:** RBWH

**STATEMENT OF CONDUCT:** This study will be performed in keeping with the NHMRC Australian Code for the Responsible Conduct of Research 2018 and the ICH Guideline for Good Clinical Practice.

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Contents

[Project Team Roles & Responsibilities 2](#_Toc927119681)

[Summary 4](#_Toc996670188)

[Background & Rationale 5](#_Toc813474259)

[Study Aim/s 8](#_Toc586917629)

[Hypothesis 9](#_Toc909135330)

[Participating Sites 9](#_Toc1033516288)

[Study Design 10](#_Toc1336736952)

[Primary Objective: 10](#_Toc1553435710)

[Secondary Objectives: 11](#_Toc957699375)

[Inclusion Criteria 11](#_Toc902340888)

[Exclusion Criteria 11](#_Toc210590206)

[Recruitment and Screening 11](#_Toc500574795)

[Consent Process 12](#_Toc1453591813)

[Expected Study Duration 12](#_Toc668916170)

[Data Source and Population 12](#_Toc1900980446)

[Population 12](#_Toc1813163646)

[Data sources 12](#_Toc429399237)

[Methodology 14](#_Toc1665200859)

[Outcome Measures and Definitions 15](#_Toc1760642145)

[Statistical Analyses 17](#_Toc2109796859)

[Consumer and Community Involvement 18](#_Toc141560400)

[Ethical Considerations 18](#_Toc2132526510)

[Study Procedure Benefits 19](#_Toc1167694754)

[Study Procedure Risks 20](#_Toc735629495)

[Confidentiality and Privacy 20](#_Toc1851577937)

[Data Storage and Record Retention 21](#_Toc608793074)

[Safety Reporting 21](#_Toc1678250951)

[Conflict Of Interest 22](#_Toc119070301)

[Funding 22](#_Toc768025578)

[Research Outcomes 23](#_Toc1945180619)

[REFERENCES 23](#_Toc1463436285)

# Summary

**Background and Rationale:** IBD is a chronic, inflammatory gut disorder affecting over 90,000 Australians. Symptoms and lack of access to optimal care have a major negative impact on quality of life (QoL). The Australian healthcare system faces simultaneous challenges of an aging, comorbid population, an overreliance on outdated technology, and uneven access to care in urban and regional areas. There is a need for cost and time-efficient management strategies which improve quality of care and outcomes.*CCCare* is a novel, web-based software tool that supports IBD management. *IBDSmart* is a smart phone application that assists patients to monitor their symptoms. *IBDoc* is a digital home-monitoring system for faecal calprotectin.

**Aim:** This study will compare the impact and acceptability of a digital strategy utilising CCCare, IBDSmart, and IBDoc, to standard IBD practice, in the delivery of care to patients from a regional area in Queensland, Australia.

**Primary Objectives: 1.** To determine the impact of these digital strategies on: QoL, disease symptoms, total costs of care. **2.** To assess patient, nurse and doctor usability of digital tools.

**Target Population**: Participants with IBD will be recruited from a regional clinic in Queensland, Australia from January 2024.

**Project Design and Methods:** Prospective non-inferiority study comparing use of digitally-assisted care versus standard of care (SoC) at a regional hospital. Planned sample size is 96 participants. Inclusion criteria: confirmed IBD, ≥1 outpatient appointment in last 12 months & >16 years of age. Exclusion criteria: likely/planned surgical intervention, stoma or ileal pouch-anal anastomosis, pregnancy. Study duration 15 months (3 month patient accrual, 12 month minimum follow up). Participants in intervention group to use digital strategies*: IBDSmart* (symptoms), *IBDoc* (faecal calprotectin). Results will be fed back via online portal *(CCCare)* to the clinical team. Participants in the SoC group will receive current standard care, which does not use digital strategies. All IBD care is directed by two gastroenterologists.

**Project Assessment/Evaluation:** clinical symptoms, biochemical markers of disease activity and quality of life will be assessed at baseline, 6 and 12 months. Healthcare utilisation costs will be calculated for the duration of the trial and compared to the preceding 12-month period.

**Project Outcomes:** We are implementing this strategy in a unique rural and chronically underserved population. By facilitating a treat-to-target approach, the digital strategy will improve surveillance of disease activity and reduce unnecessary outpatient review. These efficiency gains will create slots for urgent reviews if/when participants suffer a disease flare.

# Background & Rationale

Inflammatory bowel disease (IBD) is a chronic, immune-mediated gut disorder that affects over 90,000 Australians.1-3 The two main forms of IBD are Crohn's disease (CD) and ulcerative colitis (UC), which cause inflammation in the gastrointestinal tract and can lead to a range of complications, including progressive bowel damage, hospitalisation, malnutrition, and a significantly increased risk of colorectal and biliary tract cancers.4

The prevalence of IBD in Australia is increasing owing to the tandem effects of a rising incidence and the compounding effect of longer life expectancy. Australian IBD healthcare systems also face the simultaneous challenges of an aging and increasingly comorbid patient population, inadequate workforce expansion, time-consuming prescribing processes, disparate public and private pathology and healthcare systems, an overreliance on outdated technology and an unequal distribution of funding and expertise.5 These factors are culminating in clinical staff burn-out as well as poor patient care and necessitate more cost- and time-efficient IBD management strategies.

Healthcare in Australia is not equitable, with those in regional, remote and rural (RRR) communities at higher risk of poor health outcomes compared to those in metropolitan Australia as a result of geographical isolation, shortage and high turnover of healthcare providers, socioeconomic disadvantage, greater difficulties in transport and communication and sparsely distributed populations, leading to diseconomies of scale.6In Australia, it is estimated that 40% of IBD patients live in RRR areas7, many of whom are required to travel long distances to receive regular biologic drug infusions, endoscopy, imaging and outpatient review. Frequently, these healthcare interactions require an overnight hospital stay after driving or flying to a specialist urban centre, which results in patients taking time away from families and work.

The direct and indirect costs to IBD patients and the Australian healthcare system are considerable: in 2012, PwC estimated that hospital costs attributable to IBD were in the order of $100 million, productivity losses (including loss of earnings, absenteeism and premature death) totalled more than $361 million and other costs associated with taxation revenue impact, carer costs, out-of-pocket expenses, deadweight losses, welfare costs and loss of wellbeing at over $2.7 billion for the year.8

The implementation of digital healthcare may offer an innovative solution to redress the inequity of IBD care in RRR locations. Digital healthcare is the collective term for the use of different technologies, devices and information systems to deliver modern healthcare. Examples include telemedicine outpatient reviews as well as mobile applications (“apps”) and patient portals which enable capture and remote monitoring of patient reported outcomes (e.g. disease symptoms, quality of life (QoL) scores, depression and anxiety scores), quality of care metrics (e.g. corticosteroid use, drug safety monitoring and colonoscopy surveillance) and point of care test results (e.g. faecal calprotectin [FCP]).

FCP is used routinely in primary care to differentiate irritable bowel syndrome (IBS) from IBD. It also fulfils an important non-invasive role in monitoring response to therapy which correlates with endoscopic targets of treatment.9 Current standard of care predicates that a stool sample has to be taken by the patient to either their GP, a private pathology collection centre, or a hospital to have this test processed in a laboratory. The result can take approximately 10-14 days to be returned with no automated process for the patient to view their own test result nor for clinicians and nurses to view the result. This risks important information being delayed or missed. Bühlmann Laboratories have developed a reliable Point of Care (POC) test that can be performed at the patient’s convenience at home, and read by advanced smart phones, delivering an instant result to the patient and communicating it directly to their care team. The application and web portal together constitute IBDoc. This system has now undergone testing for acceptability and validity in Europe.10,11

A previous New Zealand study which randomised patients to either a digital monitoring strategy using smart phone capture symptoms (IBDsmart) and FCP (IBDoc) or standard of care found that that digital monitoring reduced costs and was non-inferior for QoL and symptom scores at 12 months as compared with standard of care.12 Other studies have shown that treatment escalation based on symptoms and faecal/blood biomarkers of inflammation are superior to symptoms alone. These biomarkers can be used as proxy measures of mucosal inflammation to guide a treat-to-target approach and deliver better long-term disease outcomes. Systematic reviews comparing the use of digital healthcare to standard of care in IBD suggest that they reduce healthcare utilisation and save money, although they may not be more effective than traditional encounters in improving disease activity, QoL, or treatment adherence. However, whilst the COVID-19 pandemic accelerated the use of digital healthcare, the uptake is far from widespread: in an IOBD survey of 56 countries with 802 responses, only 6% of centres reported regular use and 13% occasional use of telemedicine.13 One limitation of use of multiple digital tools is that each system requires a clinician to access a different online portal to access patient results, thereby failing to maximise on the potential efficiency savings.

Australia and New Zealand (ANZ) have developed one of the largest IBD-specific electronic medical records (EMR) to date, called Crohn’s Colitis Care (CCCare). This cloud-based patient management platform is equipped with a consumer-facing portal and back-end clinical registry. Since 2018, CCCare has been deployed at over 20 ANZ sites, recording real-world data in real-time for over 13,000 people with IBD. Crucially, CCCare is used in everyday clinical practice and therefore captures longitudinal data, unlike static patient registries. Furthermore, unlike many new healthcare apps, CCCare will enable the direct linkage of patient entered data back to the cloud-based portal which is already used by specialists in the routine clinical care of patients. This overcomes isolated silos of patient data with multiple proprietary systems and user logins which hinder usability and utility. Patients can be educated to use the output from their smart phone symptom apps and point of care biomarkers to self-manage their condition by adjusting the dose of their medications; empowering patients in self-management of their chronic condition was a key area of need identified by the Australian Inflammatory Bowel Disease National Action Plan (2019).14 A further key advantage to digital healthcare is the capture of rich datasets, which can be analysed through artificial intelligence and machine learning strategies to improve IBD care for the future. These data can be used to drive automation of routine tasks currently performed by healthcare professionals which suffer from human error and reduce time available for direct clinical care. It is currently unknown if poor computer literacy, poor internet access or simply patient preference will limit the implementation of digital healthcare in Australia.

We seek to address the methodological shortcomings of previous digital health studies by implementing digital strategies alongside IBD service re-design, integrating smart phone apps with CCCare, using standardised disease outcome measures, engaging with clinicians and patients in service re-design, adopting previously validated apps and point of care technologies and providing a full cost-benefit analyses including indirect costs to patients.

## Study Aim/s

This study aims to assess the acceptability and impact of implementing a new digital strategy utilising CCCare to deliver a treat-to-target approach in IBD patients from a remote and regional location in Queensland, Australia.

## Hypothesis

Implementation of the digital strategy reduces costs and is non-inferior to standard of care in terms of both patient disease activity and quality of life when assessed at 12-months.

## Participating Sites

The Royal Brisbane and Women’s Hospital is a quaternary hospital in Brisbane, Australia which cares for approximately 2,000 urban patients as well as 350 patients located at a regional hospital in Rockhampton, Queensland. All patients at the regional centre are reviewed using telemedicine appointments rather than face to face clinics.

## Study Design

This study is designed as a randomised controlled trial at a remote and regional hospital in Queensland

**Figure 1:** Illustration of study design



QoL = quality of life

## Primary Objective:

The primary objective of this study is to evaluate whether the implementation of a digital monitoring strategy utilising validated smart phone and cloud-based clinical tools enables safe, effective, and cost-efficient care for IBD patients living in a regional location in Queensland, Australia, as compared to current standard of care. To achieve this objective, we aim to evaluate what the impact the real-world implementation of the new digital strategy has on **i) patient QoL ii) disease symptoms iii) total costs of care** (direct healthcare and indirect patient costs) in the 12 months following its implementation.

## Secondary Objectives:

We will also explore the following secondary objectives, comparing the intervention arm implementing digital tools versus the standard of care arm:

1. To investigate what impact the digital strategy has on **disease outcomes** (proportion of patients with disease flares; IBD-related hospital admissions; emergency visits and surgeries; and corticosteroid use) and **disease activity** (proportion of patients in endoscopic and/or biomarker remission).
2. To assess **patient, nurse and clinician acceptability** of the new digital remote monitoring strategy overall and specifically the following two components:
	* 1. IBDsmart (patient symptom smart phone app)
		2. IBDoc (home FCP monitoring smart phone app)
3. To compare **prescribing differences** in the use of intravenous vs. oral/subcutaneous advanced therapies as well as escalated dosing between the two cohorts
4. To compare the **uptake of point of care FCP** testing (the number of different patients submitting a FCP test and the number of FCP tests submitted by each patient)
5. To **compare correlation** of home FCP test (IBDoc) with standard laboratory ELISA for FCP
6. To determine patient and disease factors associated with **good engagement with remote monitoring**

## Inclusion Criteria

1. confirmed UC, CD or IBD-U
2. at least 1 outpatient appointment in the last 12 months
3. willing and able to provide written consent
4. ≥ 16 years of age

## Exclusion Criteria

1. likely/planned surgical intervention
2. ileostomy, colostomy, or ileal pouch–anal anastomosis
3. pregnant

## Recruitment and Screening

The RBWH hospital iEMR will be used to generate a list of all IBD patients at Rockhampton hospital under the care of the RBWH IBD team. This list will be screened against inclusion and exclusion criteria by the study research nurse and/or by study clinician.

## Consent Process

A cover letter and study participant information sheet with a copy of the consent form will be sent to all eligible participants in 3 ways to inform them about the study, via: letter in post, SMS message and email.

Posters advertising the study with a Quick Response (QR) code to the study information sheet will also be placed in the hospital day infusion units (where some patients attend for drug administration), as well as outpatient and endoscopy units. It should be noted that all patients in these locations are already reviewed entirely within a telemedicine clinic, and therefore some patients do not attend the hospital at all to receive care.

Further opportunities to discuss the study will be taken at routine follow up outpatient clinics leading up to the study commencement. 1-2 weeks after sending patients communication about the study, a research nurse or a clinician will then call each patient to see if they are interested in participating. Interested and eligible patients will be taken through the eConsent process. A signed copy of the consent form will be emailed out to participants. A printed version of this consent form and the patient information sheet (PIS) used will be kept at the RBWH IBD research office along with other site and study documents. The office is located at the RBWH, Ned Hanlon Building, Level 9. All hard copies will be stored in a locked filing cabinet in a locked office within the Gastroenterology unit at RBWH.

## Expected Study Duration

The total study duration is anticipated to take 15 months including: a 3-month accrual period and a minimum of 12-month follow up.

## Data Source and Population

### Population

The RBWH is one of five hospitals in Metro North Hospital and Health Service (HHS) and is the largest tertiary referral hospital in Queensland, with nearly 1000 beds and more than 6000 multidisciplinary staff. Most people treated at RBWH live in areas outside the primary service catchment area. Residents of the Wide Bay and Central Queensland HHSs are also referred to the RBWH IBD specialist telehealth programme by their GP or secondary care clinician in a regional hospital. All telehealth patients are reviewed via the online Metro North Telehealth Portal. Rockhampton is the main hospital serving Central Queensland HHS. Some IBD patients living within the Rockhampton catchment area may choose to have their care delivered by their GP and/or a private gastroenterologist – data for these patients will not be captured.

### Data sources

The following sources will be used to collected data as per the Table 1.

**Table 1:** Data collection

|  |  |
| --- | --- |
|  | **Timepoint** |
| **Study Component** | **0 month** | **6 months** | **12 months** |
| Confirmed Study Eligibility | x |  |  |
| Informed consent | x |  |  |
| IBD Medications | x  |  |  |
| Concomitant medications | x  |  | x |
| **Biomarkers** |  |  |  |
| Blood tests (FBC, Chem20, CRP, IS, vitamin D, B12, folate, 6TGN levels, IFX and ADA drug levels) | x |  | x |
| Faecal calprotectin (lab ELISA) \* | x |  | x |
| Faecal calprotectin (IBDoc) \* | x (digital arm) | x (digital arm)  | x (digital arm) |
| **Symptoms** |  |  |  |
| SCCAI | x | x | x |
| HBI | x | x | x |
| FACIT-F | x | x | x |
| **Quality of Life** |  |  |  |
| IBDQ | x | x | x |
| EQ5D | x | x | x |
| **Costs** |  |  |  |
| Work Productivity and Activity Impairment questionnaire (WPAI) | x | x | x |
| Participant Health Care Utilisation Questionnaire | x | x | x |
| Pharmaceutical Benefits Scheme (PBS) utilisation |  |  | x |
| Medicare Benefits Schedule (MBS) utilisation |  |  | x |
| **Acceptability**  |  |  |  |
| Patient satisfaction with care | x |  | x  |
| Patient acceptability of IBDsmart and IBDoc apps and monitoring |  |  | x (digital arm) |
| Nurse and doctor acceptability on acceptability of using digital monitoring and apps  |  |  | x (digital arm) |

\*patients randomised to digital arm will be able to submit home faecal calprotectin and symptom score at their discretion between these time points.

**Patient demographic and disease phenotype data** will be extracted from patient electronic medical records (RBWH iEMR and CCCare).

Patient IBD-related healthcare service utilisation (endoscopy, outpatient, inpatient, radiology, emergency department presentations) data will be extracted from patient electronic medical records (RBWH iEMR and CCCare).

**Disease symptom data** will be collected using the smart phone app (IBDsmart) and paper questionnaires at baseline, 6- and 12-months in the digital and standard of care cohorts, respectively. Additionally, symptom data can be entered by the digital cohort using their smart phone and the IBDsmart app at any other time during the study.

**Disease activity biomarker data** will be extracted from IBDoc (home FCP test) and standard laboratory ELISA (lab FCP test) at baseline, 6- and 12-months. Additionally, a home FCP test can be entered by the digital cohort using their smart phone and the IBDoc app at any other time during the study. Blood tests will be captured from public and private pathology databases (MyHealth, Queensland Pathology, Sullivan and Nicolaides, QML).

**Quality of life data** will be collected using online electronic questionnaires (RBWH RedCAP instance), or where not possible due to technology/internet connection, paper questionnaires at baseline and 12-months in the digital and standard of care cohorts.

**Patient acceptability** datawill be collected by asking participants in digital cohort to give their opinion on participation in the digital programme, as well as the use and acceptability of the IBDoc and IBDsmart apps. Each item was scored on a five-point Likert scale ranging from strongly agree to strongly disagree.

**Clinician and nurse acceptability** datawill be collected by asking participants in digital cohort to give their opinion on participation in the digital programme.

## Methodology

Eligible patients will be randomized after enrolment in a 1:1 ratio. Randomisation will be stratified by disease type (CD vs. UC/indeterminate colitis) and disease activity (remission vs. active disease) at the time of randomisation. Two clinicians will manage both the digital and standard of care cohorts and will swap between the cohorts after 6-months to attempt to minimise the influence of the clinician on the outcomes.

The digital strategy monitors patient symptoms and faecal calprotectin using IBDsmart and IBDoc, respectively. These data will be automatically relayed to a clinical dashboard within CCCare that will be viewed every weekday by the RBWH IBD team to direct patient care. Patients receiving standard of care will be reviewed in a telemedicine clinic alongside pathology and standard laboratory faecal calprotectin. The frequency of follow-up appointments and pathology testing will be at the treating clinician’s discretion. The mandated frequency of biomarker monitoring in both cohorts is shown in Table 1.

The IBDsmart app is a symptom monitoring app which contains validated questionnaires for measuring IBD symptoms. The symptom questionnaires available to UC patients will be the Simple Colitis Clinical Activity Index (SCCAI). The questionnaire asks about bowel frequency, urgency, blood, general well being & extra colonic features. Participants will be able to select the appropriate answer from a checklist. The symptom questionnaires available to CD patients will be the Harvey-Bradshaw Index (HBI). The questionnaire asks about general well being, abdominal pain, number of liquid stools, presence of an abdominal mass, and extra-intestinal symptoms. Participants will be able to select the appropriate answer from a checklist. 15,16 Each questionnaire will take approximately 2 minutes to fill out and participants will be asked to fill out the questionnaire on entry to the study, at 6 months and 12 months.

The IBDoc app provides a means of patients measuring their faecal calprotectin level at home by using a lateral flow device that produces an output which the smartphone takes a picture of to give a score. Participants will be asked to extract a faecal sample into a test tube using the stool extraction kit supplied. The stool is then released from the tube into a test cassette. Using the camera the participants Smartphone, the test cassette is scanned and a quantitative result of faecal calprotectin in provided. These data will be automatically relayed to a clinical dashboard within CCCare that will be viewed every weekday by the RBWH IBD team to direct patient care. The faecal calprotectin test is expected to take 2-4 minutes to perform. Participants will be asked to perform the test on entry to the study, at 6 months and 12 months. The IBDoc has been shown to have an R2 of > 0.85 versus the normal laboratory methods.17

## Outcome Measures and Definitions

The following outcomes and definitions will be used in this study:

The co-primary symptom endpoint of this study is the proportion of patients in clinical remission as defined by their modified Harvey-Bradshaw index (mHBI; which excludes the abdominal examination component of standard HBI score) or SCCAI above at week 52. Secondary endpoints include change in symptom scores from baseline at 52 weeks and the proportion of time spent in clinical disease remission in the 3-months prior to and 12-months after the digital transition in the remote monitoring cohort.

**Disease symptom data:**

The mHBI is an activity index that rates overall well-being, abdominal pain, number of liquid stools per day and EIMs. As compared with the original HBI, the mHBI removes the need for physicians to physically examine patients for an abdominal mass. Scores <5 are indicative of symptomatic remission; scores ≥ 5 = indicate active disease: Mild = 5-7, Moderate 8-16 and Severe >16.

The SCCAI (also known as the Walmsley index), and the mHBI, will be used to record disease symptom scores for UC/IBDU patients, and CD patients, respectively.15,16 SCCAI is an activity index used to assess disease activity for patients with UC/indeterminate colitis. The SCCAI is a subjective activity index that rates overall well-being, daytime, and nocturnal bowel movements, urgency, rectal bleeding and EIMs. Scores <3 are indicative of symptomatic remission; scores ≥ 3 indicate active disease.

FACIT-F is a functional assessment of chronic illness therapy-fatigue. It has demonstrated reliability and validity in the IBD cohort.

**Disease activity data:**

Blood and stool biomarkers will be collected as per routine clinical practice but mandated at 0, 6 and 12 months for both cohorts. Blood tests will include a complete full blood count (FBC), comprehensive metabolic profile (chem20), and C-reactive protein (CRP). A CRP <5mg/L will be used to denote inactive disease.

Faecal calprotectin will be collected in accordance with routine clinical care in the SoC cohort, whereas all patients in the digital cohort will be asked to submit a POC faecal calprotectin test as 0-, 6- and 12-months or at patient discretion at time of a change in symptoms concerning for a flare of their disease. A laboratory or home POC faecal calprotectin <150 ug/g (UC and ileal CD) or <250ug/g (ileocolonic CD) will be used to define biomarker inactive disease.

A composite definition of **biomarker remission** will be used: a laboratory or home POC faecal calprotectin <150 ug/g (UC and ileal CD) or <250ug/g (ileocolonic CD) AND CRP < 5.0 mg/L.

A **disease flare** will be defined as disease activity necessitating therapy intensification [including steroid therapy, exclusive enteral nutrition, aminosalicylate dose escalation or introduction of biologic treatment]

**Quality of life:**

Assessment of Quality of Life and disease-specific QoL will be assessed with the IBD Questionnaire (IBDQ) and EuroQoL 5-dimensions (EQ-5D)

The IBDQ has been validated previously for IBD and correlates with disease activity indices. A score >168 correlates with remission in patients with CD. Changes from baseline of 16 to 32 are clinically meaningful.

The EQ-5D is an instrument which provides a global value for HRQoL, with 5 questions related to 5 dimensions: mobility, selfcare, usual activities, pain or discomfort, and anxiety or depression.

**Total costs of care:**

Data for calculation of **direct costs of healthcare** utilisation will be extracted from the electronic medical record (iEMR), CCCare and EQ-5D. Specific service utilisation parameters include:

* Outpatient usage (scheduled visits to a gastroenterologist, colorectal surgeon or IBD nurse)
* IBD-related hospitalisations, surgeries and emergency department visits
* Number of days of inpatient admission
* Number, type and location of endoscopic assessments
* Use of infusion centres for IV therapies
* IBD telephone helpline usage
* IBD email helpline usage
* Use of escalated dosing of advanced therapies
* Number, type, and location of radiological assessments

To accurately capture data on medication and medical procedure utilisation, data will be requested from Services Australia. Specifically, data will be requested from Pharmaceutical Benefit Scheme (PBS) to accurately capture medication utilisation, and the Medicare Benefits Schedule (MBS) to capture medical procedure utilisation. The data will be collected at the conclusion of the trial (12 months post-baseline).

**Indirect costs of healthcare** will be calculated using Work Productivity and Activity Impairment questionnaire (WPAI) at 0, 6 and 12-months.18 This questionnaire comprises 6 questions on the effect of the disease on work and activities of daily living during the previous 7 days. A higher score on the questionnaire indicates a more pronounced effect on work and daily activities.

**Patient, nurse, and doctor acceptability**

We will collect data to evaluate the acceptability of i) digital monitoring as compared with their previous care and specifically feedback on acceptability of the IBDoc and IBDsmart apps and devices. We will utilise previously designed questionnaires which use Lickert scales to assess responses.

## Statistical Analyses

Power calculations determined that a sample size of 31 patients with CD per group (n = 62) at follow-up would provide 80% power to detect noninferiority (P < 0.05) using the HBI, assuming an SD of 4.7 and an equivalence limit of 3. In addition, a sample size of 17 patients with UC per group (n = 34) at follow-up would provide 80% power to detect noninferiority (P < 0.05) using the SCCAI, assuming an SD of 3.5 and an equivalence limit of 3. Finally, a sample size of 45 patients with either CD or UC per group (n = 90) at follow-up would provide 80% power to detect noninferiority (P < 0.05) using the IBDQ, assuming an SD of 38 and an equivalence limit of 20. Thus, the study will be adequately powered, with a total of 96 participants (62 with CD and 34 with UC) at follow-up.

Mean disease scores and standard deviations will be calculated within disease type (HBI or SCCAI) at each visit. Change from baseline will also be compared within and between groups at each visit. Identical analyses will be used for QoL scores by disease type and for all participants. Comparisons will be made of groups on change from baseline at each visit for disease activity and QoL using a mixed model repeated measures approach, to account for within person correlation.

A cost-utility analysis will be undertaken with the primary analysis from the perspective of the healthcare system. This perspective is the most commonly used economic evaluation method in Australia for policy makers and will allow comparisons across other sectors to identify the relative cost-effectiveness of the intervention for funding proposals. An incremental cost-effectiveness ratio will be calculated following the formula:

$$ICER=\frac{Cost\_{int}-Cost\_{usual}}{QALY\_{int}-QALY\\_usual}$$

Where int is the new intervention, usual represents usual care and QALY stands for quality adjusted life year. Cost of the intervention will be calculated based on time for the nurse and gastroenterologist to monitor and complete treat-to-target based care. Cost of health care usage will be calculated from iEMR electronic hospital records. Unit costs of care will be derived from appropriate sources for the care. Other costs will be applied at appropriate wage standards for the care provided.

Utility scores will be derived from the EQ-5D-5L19 using the Australian algorithm20. Quality adjusted life years for each group will be calculated using the utility score multiplied by time in the study.

Cost-utility will be modelled using techniques appropriate for clustered data, such as a bivariate GEE (Generalised Estimating Equation) with robust standard errors which can adjust for the clustering and non-normal nature of the data (5). A final parsimonious model will be selected following data examination and measures of model fit. One-way and probabilistic sensitivity analyses using bootstrapping will be conducted to explore variability in the sampling and population.

# Consumer and Community Involvement

We have invited a panel of 10 patients from a remote and regional clinic to an online meeting attended by clinicians and nurses involved in the study design and set up. During this session patients were first given a presentation on the study design and then invited to give feedback. We also demonstrated both patient apps (IBDsmart and IBDoc) to the patient panel. Additionally, the panel were sent all participant information sheets and the consent form with comments integrated. The panel approved the final study protocol and documents.

This study was also presented to the Queensland Gastroenterology Clinical Network for feedback and endorsement. This network consists of over 140 members with a steering committee consisting of medical officers, nurses, allied health professionals, a general practitioner, and a consumer representative.

# Ethical Considerations

The following ethical considerations are highlighted:

1. **Replacement of outpatient appointments:** The most pertinent ethical concern is the use of smartphone technology to replace a telemedicine outpatient appointment/s. However, it is believed communication between patient and doctor will be enhanced and not hindered by the two apps (IBDsmart and IBDoc).
2. **Smart phone/internet access/language barriers:** Patients who do not have access to a smartphone, are unable to utilise smartphone technology, and or patients from linguistically diverse backgrounds, will be unable to take part in this study. If successful, future versions of the apps will include non-English language instructions.
3. **Reporting tests results directly to patient:** The default setting within IBDoc (home faecal calprotectin testing app) is show the patient the numerical result of the test straight away. This default setting can be adjusted to show a traffic light system result (red, amber, green) with instruction on how to interpret the result. Alternatively, some patient may choose not to see their result after discussion with their clinician if they feel that this would cause them concern. All results are automatically sent to the IBD nurses regardless of the patient’s viewing preferences to action.
4. **Data collection and storage:** Data collected on the IBDoc app will be stored on servers in North America and Europe. The safety of this information has been independently assessed and verified by the IT department at RBWH, Metro North and Digital Implementation team at Queensland Health.
5. **Funding by pharmaceutical companies:** Some funding for this project is provided by Celltrion, a pharmaceutical company who produce biologic agents for the management of IBD. Money is provided to support this study as well as transitioning of patients from an intravenous to subcutaneous version of the same drug (infliximab). This funding is free from any data transfer or intellectual property request. No targets of patients taking subcutaneous therapy have been stipulated. Since subcutaneous infliximab entered the market prior to this study and the Celltrion funding, it has been the policy of all RBWH IBD clinicians to ask patients whether they want to switch to this route of administration. One of the main advantages of subcutaneous therapy over intravenous therapy with the same drug, is that patients are no longer required to have the drug administered in the hospital setting, instead patients or their carer/family administer the drug in their own home. This choice is discussed at length with the patient and is left to the patient to make the final decision.
6. **Handling of stool:** Participants will be required to handle their stool for the IBDoc app. However, IBD patients are accustomed to handling stool both to exclude infections at the point of flare and quantify inflammation with the existing lab based faecal calprotectin test that is used as part of existing everyday clinical practice. All participants will receive training from a registered nurse to ensure the health and safety of participants. Training will encompass test set up, safe administration, waste disposal, and hygiene. Furthermore, personal protective equipment will be provided to participants to ensure patient safety.

# Study Procedure Benefits

We expect that the digital intervention will be acceptable to patients and also non inferior to standard of care in terms of disease symptoms and quality of life after 1 year. The use of technology to automate the review of patient symptoms and biochemical results, and stratify patients according to risk, will have two key benefits: firstly, patients will experience increased surveillance of their clinical and biochemical markers of disease activity; secondly, we anticipate patients will need fewer outpatient appointments, which will be more cost-effective than the current standard of care. From the patient’s perspective, this will also reduce the need for routine reviews when they are well and create capacity for urgent review if and when they suffer a flare of their disease.

The use of automation will assist our health service to provide safer and more effective care by increasing our capacity to see new and acutely unwell patients. Our health service currently receives in excess of 50 new referrals per year from the Central Queensland region. Due to the issue of compounding prevalence, our health service is in desperate need of innovative solutions to manage the growing needs of our population.

This study is expected to facilitate care closer to a patient’s home by offering remote monitoring and empowering patients to manage their own disease through feedback of important data. This is in keeping with the current Metro North strategic plan, which emphasises the implementation of sustainable models of care that provide services in the community and/or home and reduce demand for hospital services.

The results of this study will be published in peer-reviewed journal, with a view to contributing to the continual improvement of care for IBD patients across Australia and internationally.

# Study Procedure Risks

Patients in the intervention group will be asked to handle their stools for the IBDoc app. All participants will receive training from a registered nurse to ensure the health and safety of participants. Training will encompass test set up, safe administration, waste disposal, and hygiene. Furthermore, personal protective equipment will be provided to participants to ensure patient safety.

Patients may be concerned about receiving fewer routine outpatient consultations and having reduced ability to ask questions of their treating gastroenterologist. The IBDsmart app will allow patients to submit any questions or concerns they wish to raise with their treating team. The treating team can then address the patients concerns as clinically appropriate. All patients will receive a minimum 12-monthly review of their disease even with digital monitoring.

The RBWH IBD team have a nurse led patient helpline which is currently available to all patients from Monday-Friday. Any patients in this study will still be able to contact our expert team of nurses as per existing care arrangements

# Confidentiality and Privacy

This is a clinically translatable project, with the results potentially transforming patient care across the IBD service at RBWH. As such, this project will require the collection of identifiable patient data, which will be stored on CCCare, IBDSmart and IBDoc. CCCare is already approved by RBWH for the storage of identifiable patient data. To ensure the confidentiality and privacy of patient data, the digital transformation committee at RBWH has been consulted to provide a robust review of data storage using the smartphone apps IBDSmart and IBDoc. After extensive review, both smartphone apps have been approved by the committee. The patient data collected will include patient demographics (e.g., age, gender), disease phenotype (i.e., UC, Crohn’s Disease, IBDU), symptom activity (i.e., SCCAI or mHBI), biochemical markers (e.g., CRP, FCP etc), QoL scores (i.e., IBDQ, EQ-5DL) and IBD-related service utilisation (e.g., emergency attendance, hospital admission, endoscopic and radiological tests) and disease complications (e.g., surgery, IBD-related cancer)

To ensure the confidentiality and anonymity of patients, the data will be presented in a de-identified format. The principal investigator (Dr. Gareth Walker), two associate investigators (A Prof Graham Radford-Smith & Dr. George Tambakis) and the project statistical team (Dr Gunter Hartel, Dr Satomi Okan and Katherine Hannigan) will have access to the re-identifiable data. The data will not be shared with any third-parties, including Pharmaceutical companies.

Participants who request access to their data, will be provided with a password protected personalised excel spreadsheet, containing only their own data. Data from other participants will not be shared.

# Data Storage and Record Retention

All data will be stored on a password protected hospital computer. The password protected computer will be stored in the office of the principal investigator. The data will only be accessed by the principal investigator (Dr. Gareth Walker), and the two associate investigators (A Prof Graham Radford-Smith & Dr. George Tambakis). The project statistical team (Dr Gunter Hartel, Dr Satomi Okan and Katherine Hannigan) will have access to the de-identified data, as they are not employees of Metro North.

Hard copy consent forms will be stored in the a locked filing cabinet in a locked office (RBWH IBD research office). The office is located at the RBWH, Ned Hanlon Building, Level 9.

Data will be archived for 15 years, before being destroyed. After 15 years, all digital data will be permanently disposed using overwriting. Any physical data will be shredded, and then disposed of in a confidential paper bin

# Safety Reporting

The digital technologies (IBDoc, IBDsmart) utilised in this study have all been validated in previous clinical trials. Therefore, we do not anticipate any adverse events related to these products.

The use of digital technology to automate patient care is novel. The main adverse events associated with this approach is the development of a flare of IBD and or the complications related to IBD. We assess this risk to be small as patients will be receiving increased surveillance of symptoms and biochemical markers. The risk is further mitigated by increasing our capacity to review acutely unwell patients in clinic. Furthermore, a safety net is in place whereby all patients are provided with the contact details (email and phone) of our IBD nurses and receive education on the warning signs of a flare of disease and are encouraged to make contact with our team.

Flare of disease is common in IBD patients. Mild to moderate flares can be managed in the community and does not require immediate reporting. Severe flares which require hospitalisation, and the development of complications related to IBD (e.g. obstruction or perforation) will require immediate reporting.

Each patient will be assessed at baseline, 6 & 12 months for a flare of disease (3, 9 and 15 months for digital cohort) and development of complications. Detailed records will be kept of all adverse events. Each adverse event will be assessed and categorised.

Although highly unlikely in this study given multiple safe worldwide implementations of similar digital monitoring strategies, at 6 months we will convene a safety panel consisting of the study team and the non-study team RBWH lead for morbidity and mortality will review any adverse events maximise patient safety. If concerns are raised, then the study will be halted or terminated early.

# Conflict Of Interest

The investigators certify that they have no affiliations with or involvement in any organisation or entity with any financial interest (such as honoraria, educational grants, employment, membership, consultancies, stock ownership, or other equity in test; and expert testimony or patent-licensing arrangement), or non-financial interest (such as person or professional relationship, affiliations, knowledge or beliefs) pertaining to this study.

A portion of the funding for this project is provided by Celltrion, a Pharmaceutical company who produces biologic agents for the management of IBD. The funding provided is benevolent and free from coercion.

# Funding

The following funding sources will be used:

1. Takeda & AbbVie: we are seeking $75,000 from both Takeda & AbbVie ($150,000 in total) to fund CCCare IT integration and new digital patient monitoring portal. This well be a one off cost

2. Queensland Teletrials programme (secured): $160,000 to fund a research nurse

3. Queensland Health Digital Transformation Department (secured): $100,000 to fund IBDoc test kits

4. RBWH IBD Research funds: to cover additional set up costs (this includes a pending grant application submitted to the RBWH Foundation for $50,000).

# Research Outcomes

A lay summary of the pertinent findings from resulting publications will be disseminated to all participants by email.

The anonymised data may also be used in the future for artificial intelligence analysis in the bid to find better novel biomarkers which predict future disease flare and complications.

These data will not be made available to other researchers outside of the principal institutions (RBWH, QIMR, UQ).

The aim is for one or more manuscripts relating to this study to be published in leading gastroenterology journals. There are no contractual or other agreements or obligations with sponsors, funders, the owners of intellectual property or other parties that may influence these publication plans.

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