TrueColours: real time data collection in patients with ulcerative colitis

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University of Oxford
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A thesis submitted for the Degree of Doctor of Philosophy
To Andre and Summer
“Nil sine magno vita labore dedit mortalibus”

Horace, "Satire" 1.9.59-60
TrueColours: real time data collection in patients with ulcerative colitis
Alissa Walsh, Linacre College, Oxford
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Abstract

This thesis details the adaptation and evaluation of an e-health software platform known as TrueColours (originally developed by the Oxford Department of Psychiatry for treating bipolar disorder) for use in ulcerative colitis (UC). The resulting web-based programme, TrueColours UC, is capable of recording symptoms, quality of life (QoL), biomarkers, blood, endoscopic and histopathological results as well as internationally agreed patient-reported outcome measures (PROMs). The approach involved a pilot followed by qualitative analysis of system usability and quantitative analysis of symptom patterns and decision-making to develop a predictive index.

TrueColours UC was piloted for 6 months in 66 patients. Feasibility testing revealed adherence rates to daily and fortnightly questionnaires of 76% and 95% respectively. The retention rate at 6 months was 86%. Mixed methods analysis on system usability identified minor areas for improvement. Qualitative interviews revealed that by using TrueColours UC, patients felt empowered, expressed by an increased awareness, control over decision-making, reassurance and communication.

Logistic regression models for predicting escalation of therapy at an outpatient appointment were developed. These models revealed that remotely collected symptom information can largely predict whether escalation of therapy will occur. External validation is necessary, but this model has the potential to improve resource utilisation.

Analysis of longitudinal repeated measurements allowed novel exploration of validated indices for symptoms and QoL. A simulation model estimated the information loss that occurs when intervals between data entry are increased. A new method for phenotyping disease pattern was identified. Cut-off levels for faecal calprotectin in remission and active disease are proposed.

Involving patients in collecting PROMs has the potential to change disease management pathways, identify patients for trials and provide insight into the biology of the disease.
Acknowledgements

This thesis is the fruit of my labour, but it would not have been possible without the extraordinary support of a number of people.

I am deeply grateful to my supervisors, Professor Simon Travis, Professor Gary Collins and Dr Michele Peters. In particular, Professor Travis has been immensely patient with my countless drafts and constant emails. His insight, high standards and unflagging support have been invaluable.

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I would like to thank all the Principal Investigators for their involvement in this pilot: Professor Satish Keshav, Dr Oliver Brain, Professor Holm Uhlig, and Professor Alison Simmons. I would also like to thank the Clinical Trials Nurses and the Oxford Research Nurses for Immunology and Inflammatory Diseases (ORNIID) and for their support during the trial. I truly could not have managed without you all. Also, a thank you to Marta Jagielowicz for processing the research samples.

I would like to thank the patients involved in the TrueColours UC pilot. I am so grateful for your participation and feedback.

I would like to thank my parents who, as always, have been extremely supportive. Lastly, but most importantly, I would like to thank my amazing husband, Andre, and our daughter Summer. Andre, you have been there every step of the way with a smile, enthusiasm, guidance, love and support, let alone reading the entire manuscript and offering many insights! I could not have done this without you.
Statement of originality

All work in this thesis is my own unless otherwise stated. The ideas for the theme of this thesis and the analysis from the TrueColours UC dataset were my own. The TrueColours team at Warneford Hospital, Oxford performed the technical aspects of the adaptation to TrueColours UC and provided technical support throughout the pilot.

The TrueColours UC pilot protocol, all associated forms and ethics submission were drafted and finalised by me. All TrueColours UC pilot patients were recruited and supported by me. The Clinical Trials Nurses and ORNIID gave support for scheduling, sample collection and data entry. All qualitative interviews and analysis were performed by me.

The first drafts of all chapters were written by me and then critically appraised by my supervisors. I acknowledge the work of Gary Collins and Andrey Kormilitzin who performed statistical analysis for Chapters 6 and 7.

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<td>5-ASA</td>
<td>5- Aminosalicylic acid</td>
</tr>
<tr>
<td>95% CI</td>
<td>95% confidence interval</td>
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<tr>
<td>API</td>
<td>Application Processing Interface</td>
</tr>
<tr>
<td>App</td>
<td>Application (to be used on a smartphone)</td>
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<tr>
<td>ASRM</td>
<td>Altman Self Rating Mania Scale</td>
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<td>ASUC</td>
<td>Acute severe ulcerative colitis</td>
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<tr>
<td>CD</td>
<td>Crohn’s disease</td>
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<td>CUCQ-8</td>
<td>Crohn’s Ulcerative Colitis Questionnaire – 8 questions</td>
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<td>ECCO</td>
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<td>e-health</td>
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<td>ePROM</td>
<td>Electronic patient-reported outcome measure</td>
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<td>EPV</td>
<td>Events per variable</td>
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<td>FCal</td>
<td>IBDoc® faecal calprotectin measurement</td>
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<td>IBD</td>
<td>Inflammatory Bowel Disease</td>
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<tr>
<td>IBDoc®</td>
<td>Faecal calprotectin home test produced by Buhlmann Laboratories</td>
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<tr>
<td>ICHOM</td>
<td>International Consortium for Health Outcomes Measurement</td>
</tr>
<tr>
<td>iOS</td>
<td>Operating system used for mobile devices manufactured by Apple Inc</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
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<tr>
<td>ISPOR</td>
<td>International Society for Pharmacoeconomic and Outcome Research</td>
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<tr>
<td>MP</td>
<td>Dr Michele Peters</td>
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<tr>
<td>NHS</td>
<td>National Health Service</td>
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<tr>
<td>OR</td>
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<tr>
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<td>QIDS-SR</td>
<td>Quick Inventory of Depressive Symptomatology – Self Report</td>
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<td>Quality of Life</td>
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<tr>
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<td>Randomised Controlled Trial</td>
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<tr>
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<tr>
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<td>Repeated measurements correlation</td>
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<tr>
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<td>Standard deviation</td>
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<td>TrueColours Ulcerative Colitis</td>
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<tr>
<td>UC</td>
<td>Ulcerative colitis</td>
</tr>
<tr>
<td>UCLA</td>
<td>University of California, Los Angeles</td>
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1 Chapter One

Introduction, Literature review and aims of thesis

1.1 Introduction

Inflammatory bowel disease (IBD) is a group of chronic inflammatory conditions of the colon and small intestine. Ulcerative colitis (UC) and Crohn’s disease (CD) are the principal types of IBD. While CD can affect any part of the gastrointestinal tract, UC only affects the colon, which means that the characteristic symptoms (bloody diarrhoea and urgency) more accurately reflect the biological extent of inflammation.

UC is a lifelong condition, most commonly presenting in young adults, adolescents and children. The cause of UC remains unknown. There is genetic predisposition (1) however environmental triggers must be important since the incidence has been rising in developing countries undergoing rapid industrialisation and urbanisation (for instance China and India), which cannot be due to genetic change (2). The main symptoms are urgent and frequent diarrhoea, often with rectal bleeding. In some patients, there is associated inflammation of the joints, skin, eyes, or other organs, suggesting that it is a systemic inflammatory disease (3).

UC follows an unpredictable relapsing and remitting course, with variation in the pattern and complexity of symptoms (4). Quality of Life (QoL), defined as “a global measure of patient’s perceptions, illness experience, and functional status that incorporates social, cultural, psychological, and disease-related factors”(5), can be significantly impaired in patients with UC (6, 7). Education, employment, relationships and family life may all be disrupted by the unpredictable course of the disease. This can affect self-esteem and social functioning (8).
Patients with severe disease may develop complications which are potentially life-threatening, such as perforation of the bowel. Patients with extensive disease have a long-term increased risk of colorectal cancer (9).

There is currently no cure for UC. Medical treatment for IBD has improved in recent years, but current efforts remain ameliorative rather than curative. Medications such as aminosalicylates (5-ASA), prednisolone, immunosuppressants (azathioprine, mercaptopurine, methotrexate) and biologics (adalimumab, golimumab, infliximab, vedolizumab) are used in varying combinations with the aim of inducing and then maintaining remission (10). A quarter of patients with UC are admitted to hospital at least once and these patients have a 40% chance of colectomy during their disease course (11). Recent studies show that tight control of disease activity and early intervention in the case of recurrence of intestinal inflammation are important to shorten flare duration and prevent complications (12).

Affecting males and females equally, it is estimated that over 300,000 people in the UK have UC (13). UC requires individuals to seek healthcare repeatedly over many decades. As a result, the lifetime medical costs associated with the care of a person with UC can be comparable to those with diseases such as diabetes, asthma or cancer. Estimates from 2011 revealed that the annual cost of IBD in the UK was approximately £470 million (14). Furthermore, UC has a major adverse impact on the economic contribution of many young people through the loss of productive work (15). There are strong arguments both clinically and economically for focusing services towards prompt detection and optimal out-patient management of disease exacerbations and effective maintenance of remission.
Conventional monitoring and management of patients with UC revolves around assessment during brief clinic visits several weeks or many months apart. These visits are often scheduled in advance but given the unpredictable nature of the disease, flares are often discordant from scheduled visits. Given the increasing incidence of IBD (13, 16, 17), this will no doubt continue to put significant strain on health care capacity. Urgent visits can be scheduled when symptoms develop, but limited clinic capacity can result in long delays in diagnostic testing and initiation of therapy (18). This does not seem to be the best way of managing or understanding the impact of relapsing and remitting inflammatory disease.

Health authorities have in recent years focused on the development of tele-based services in the belief that they will offer cost-effective solutions. Tele-medicine, digital data collection or electronic health (e-health), are technology driven innovations that may enhance the quality of care for patients with IBD (19). The question is whether hope meets expectation. e-health in the form of web-based therapy has been successfully developed for other chronic diseases such as asthma (20), diabetes mellitus (21, 22), congestive heart failure (23, 24), hypertension (25) and anticoagulation disorders (26). Interventions based on e-health reports have shown a combination of improved disease course, optimised patients' self-adherence, compliance, QoL, and reduced healthcare costs. There is increasing evidence that direct involvement of health care providers, promotion of patient empowerment and integrated care improve the outcome of chronic diseases (27, 28). Digital data are a vehicle for delivering these goals, but their complexity and lack of usability can also defeat the goals.

For IBD health care teams, the key question is how to use digital data collection better to engage our patients in their care in a way that has been achieved in other chronic diseases. Involving patients in real-time, digital data entry to which both patient and health care team
have access, seems an ideal way to empower the patient. It has the potential to provide a more accurate account of disease fluctuation, documenting the pattern of symptoms and biological disease activity over time that may result in more responsive care.

UC is a paradigm for such an approach: the disease usually affects a young and technologically literate patient population. Such an e-health programme would not only allow access to symptoms in real time to be used by the health team to improve care, but would also provide an opportunity to analyse information trends, establish thresholds and determine their relationship to objective markers of inflammation.

The programme that has been developed to try to achieve these aims is called TrueColours Ulcerative Colitis (TrueColours UC). This real time digital data collection technology as a component of clinical care is at an early stage of development. This is true not only within the Oxford clinical environment, but at a national and international level. It has, however, been pioneered and used for many years in Oxford in Psychiatry for the clinical management of bipolar disorder, a condition that relapses and remits in an unpredictable way, similar to UC.
1.2 Literature Review

This introductory literature review is divided into the following sections:

- Results from the UK IBD Standards presenting benchmarks for IBD patient care, highlighting how technological advancements might assist meeting these standards (29)
- Review of currently available e-health technologies in the context of IBD
- An overview of the TrueColours Bipolar Disorder (TrueColours Bipolar) platform, from which TrueColours UC was adapted

1.2.1 UK IBD Standards

Deficiencies in IBD care were recognised by the first national UK IBD Audit in 2006 (30). This was commissioned by the Health Foundation (31) at the instigation of the audit committee (led by Professor Jonathan Rhodes) of the IBD section of British Society of Gastroenterology. This was prompted by data from a district general hospital in the UK home counties in 2001 which had identified a mortality rate (24%) from acute severe ulcerative colitis (ASUC), identical to that in the placebo group of patients in the randomised, placebo controlled trial of steroids by Professor Sidney Truelove from Oxford in 1955 (32, 33).

Seventy-five percent of hospitals in the UK voluntarily submitted data to this audit, which found substantial variation in the provision, organisation and clinical quality of IBD services. As a result, 10 IBD Standards were agreed upon by a working group of specialists and patient representatives from Crohn’s Colitis UK (the UK IBD patient organisation) (34). Three subsequent audits, adopted by NHS England, have demonstrated improvement in process (provision of IBD nurses, dedicated gastrointestinal wards, guidelines for management for ASUC and telephone access to IBD advice), but have been unable to audit outcomes, since
there have been no agreed metrics for outcomes in IBD. Despite (or because of) national audits, it is known that almost half of IBD services in the UK do not have a database of their IBD patients and patient involvement in service development is low (35). Since the UK has embraced audit to evaluate national practice in contrast to many other countries (36) the situation outside the UK is likely to be similar or worse.

The overall strategy for improving IBD services and care requires action at local, regional and national levels. The current UK IBD Standards encourage IBD services to be knowledge-based, engaged in local and national networking, based on modern technology and to meet the specific minimum standards.

The current IBD Standards are:

- Standard A: High quality clinical care
- Standard B: Local delivery of care
- Standard C: Maintaining a patient-centred service
- Standard D: Patient education and support
- Standard E: Data, information technology and audit
- Standard F: Evidence-based practice and research

Standards C, D and E are particularly relevant to this thesis. Standard C aims to encourage patient centred-care that is responsive to individual needs and to offer a choice of care strategies where possible and appropriate. Standard D aims to empower patients to understand their condition and its management, thus allowing patients to achieve the best possible QoL. The implementation of this standard includes self-management strategies. Standard E aims for the systematic and structured collection of data. Monitoring symptoms and outcomes of treatment should lead to the reduction of outpatient appointments and
hospital admissions, but this has not been proven in the UK, or elsewhere. These nationally agreed, multidisciplinary UK standards, however, encourage the future development and use of technology to allow patients to access their personal data to support self-management.

1.2.2 e-health technologies in IBD

e-health technologies are predicted to revolutionise care delivery and patient engagement in many chronic diseases. By using technology, patients can participate in their care by signalling health outcomes during year round monitoring, setting the stage for early detection and subsequent treatment of exacerbations of disease activity (37).

We know that patients with IBD are motivated and want to be involved in their own care. A survey of over five thousand patients in six European countries and Canada showed that 88% search online for information about IBD, most doing so several times a month and two thirds expressed interest in using mobile technology to manage their IBD (IBD 2020 survey, presented to the EU Parliament 17 Oct 2013). Based on other pilot work from Mount Sinai Hospital, New York, patients cited a doctor-patient communication divide with a continued lack of goal setting and a lack of objectivity in disease control. Patients felt strongly that the impact of IBD would be significantly alleviated through better communication and support from their IBD treating team. Patients felt that e-health technologies could evaluate disease control and goals of care and were happy to be involved as partners to improve their care (38).

It is important to distinguish between the different types of technologies, methods of operation and approaches within the e-health technology space. In simple terms, e-health technologies can be in the form of an application (app) that can be used on a mobile device or
in the form of a web-based programme. An app is either a purpose-built gateway for a website (for example, an app on a mobile device that gives the user tailored access to a newspaper which would also have a website) or a specific software application that has been developed for a mobile platform alone (for example a computer game or health tracking application that is only available in that particular form on a mobile device). As a practical matter, a web-based programme provides largely the same function, but is directly accessed via a URL address and a browser rather than through the app itself. For the purposes of this thesis this distinction is one of technology rather than utility and therefore the general term e-health technology will be used.

As well as assisting with clinical care, e-health technology has the potential ability to collect large amounts of information including demographics, patient-reported outcome measures and quality of care parameters. If this patient information is entered electronically, it has been shown to have improved data quality and be more complete compared to conventional paper-pencil versions of the same instrument (39). It also allows a reduction in human resources, making routine collection of data feasible in busy clinical practice (40-43). Collecting these data on a large scale would allow comparisons between hospitals, regions, or countries, with the aim of improving quality of care.

A range of different types of e-health technologies are already available in IBD. However, a key distinction needs to be drawn as to whether or not that technology is directly connected to patient care. There are a wide variety of e-health technologies that can be accessed and downloaded onto a mobile device by a patient with IBD. These are largely personal data collection diaries (tracking symptoms, logging meals, managing medications) which do not “connect” the data entered with the patient’s hospital/clinic. While the information may be of
some utility and could be provided to the physician as part of an outpatient appointment, there is no technological or other nexus between the e-health technology and care.

A study from the Austin Hospital, Melbourne, Australia systematically assessed e-health technologies targeted at IBD patients via searches of app stores. Of the 238 products screened, 26 were assessed. Over half (54%) had diary functionalities and over a third (39%) provided health information. None offered decision support to facilitate the self-initiation of medical therapy. Only 19% had had professional medical involvement in their design (44).

A representative sample of commonly used IBD apps are:

- GI Monitor (45)
- myIBD (46)
- GI Buddy (47)

These apps act as patient diaries whereby the patient has access to their information. The patient can choose to show their treating team this information (via print outs or via email depending on which app is being used) however there is no formal integration of this information by the treating team.

It has been recognised that health system quality improvement needs patient-provider interaction to achieve improvements in care (48, 49). A literature search for e-health technologies that focus on patient-provider interaction in IBD revealed the following:

- Constant-care (50)
- UC-HAT (51, 52)
- HealthPROMISE (53)
• myIBDcoach (54, 55)
• UCLA eIBD (56)
• IBD Qorus (57, 58)

Table 1-1 gives an overview of previously developed and tested e-health tools for IBD that involve patient-provider interaction. This is followed by further information regarding each programme as well as additional programmes currently in development.
<table>
<thead>
<tr>
<th>Investigators</th>
<th>Intervention</th>
<th>IBD type</th>
<th>Study design</th>
<th>Number of patients</th>
<th>Control</th>
<th>Assessments</th>
<th>Frequency of measurements</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elkjaer et al. (Denmark and Ireland), 2010 (50)</td>
<td>Constant-care (5-ASA therapy)</td>
<td>Mild-moderate UC</td>
<td>RCT</td>
<td>333 patients randomised 1:1 (233 Denmark, 100 Ireland)</td>
<td>Standard care</td>
<td>Primary Feasibility</td>
<td>Remission: monthly Relapse: daily</td>
<td>Feasible Improved adherence Relapse shorter duration Improved QoL (Denmark only) Improved knowledge Cost saving Safe intervention</td>
</tr>
<tr>
<td>Pedersen et al. (Denmark) 2012 (59)</td>
<td>Constant-care for infliximab timing (Infliximab)</td>
<td>CD</td>
<td>Cohort study</td>
<td>27 patients</td>
<td>N/A</td>
<td>Feasibility Safety Disease activity QoL Costs Adherence Antibodies to infliximab Activity</td>
<td>Weekly</td>
<td>Feasible Safe No change in disease activity No change in QoL Cost saving Adherence 86% No difference in antibodies to infliximab</td>
</tr>
<tr>
<td>Pedersen et al. (Denmark), 2014, (60)</td>
<td>Constant-care for 5-ASA therapy (5-ASA)</td>
<td>Mild-moderate UC</td>
<td>Cohort study</td>
<td>95 patients</td>
<td>N/A</td>
<td>Primary Efficacy of 5-ASA Medication adherence Secondary QoL Patient satisfaction Faecal calprotectin levels</td>
<td>Weekly</td>
<td>Reduction in disease activity Increased medication adherence Improved QoL Satisfaction level good Faecal calprotectin reduction</td>
</tr>
<tr>
<td>Study</td>
<td>Intervention</td>
<td>Design</td>
<td>Participants</td>
<td>Intervention Details</td>
<td>Outcomes</td>
<td>Follow-up</td>
<td>Notes</td>
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<tr>
<td>Cross et al. (USA), 2012 (51)</td>
<td>UC HAT (Home tele-management system)</td>
<td>RCT</td>
<td>47 patients</td>
<td>Standard care</td>
<td>Disease activity, QoL, Medication adherence, side effects</td>
<td>Weekly</td>
<td>No difference in disease activity No difference in QoL *More than one third of patients withdrew</td>
<td></td>
</tr>
<tr>
<td>Cross et al, 2015 (61)</td>
<td>Telemedicine using mobile phone texts to communicate with patients</td>
<td>RCT</td>
<td>375 intended patients</td>
<td>Standard care</td>
<td>Primary QoL, Disease activity Secondary Health care utilisation General QoL Patient knowledge Satisfaction</td>
<td>Weekly or fortnightly</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Atreja et al. (USA), 2017 (62)</td>
<td>HealthPROMISE</td>
<td>RCT currently in progress</td>
<td>320 patients</td>
<td>Educational app</td>
<td>Symptom burden, App usage, QoL, QoC parameters</td>
<td>Fortnightly</td>
<td>Fatigue and anxiety 75% adherence at 12 months Improved QoL Increased QoC parameters</td>
<td></td>
</tr>
<tr>
<td>de Jong et al. (Netherlands), 2017 (63)</td>
<td>MyIBDCoach</td>
<td>RCT</td>
<td>909 patients</td>
<td>Standard care</td>
<td>Disease activity, medication adherence, side effects, malnutrition, smoking, QoL, depression, stress, anxiety, life events, work participation</td>
<td>Monthly</td>
<td>Less outpatient visits and hospitalisations. Higher medication adherence rates.</td>
<td></td>
</tr>
</tbody>
</table>

RCT= randomised controlled trial, app=smartphone application, QoL=quality of life, QoC=quality of care
1.2.2.1 Constant-care

Constant-care is an e-health technology that was originally developed in 2009 in Denmark for patients with mild to moderate UC (50, 64). In the event of relapse, patients were requested to log on daily and complete their disease activity score. Once remission was achieved, patients were asked to use the programme monthly until the next relapse occurred. When patients entered their symptoms online, their status appeared using a simple traffic light method: red indicated highly active UC, yellow moderately active UC, and green quiescent disease. This status was supplemented with disease activity and QoL graphs, available to both the patient and the physician. Treatment with 4g mesalazine (5-ASA) was recommended by the programme if a relapse occurred. When patients entered remission, the system then recommended a maintenance dose. Routine visits were planned as usual, but the web-patients were informed that they could cancel their appointments if they felt secure.

A randomised trial was performed in both Denmark and Ireland whereby Constant-care was compared with a control group who continued standard care in the IBD outpatient clinic, which was also compared with 106 patients in a historical cohort group. A total of 333 patients (233 Denmark, 100 Ireland) were randomised. For those randomised to Constant-care, 88% found the e-health intervention feasible (the primary endpoint), reporting that they preferred this approach to conventional care. For those randomised to the control group, 77% expressed interest in using Constant-care in the future (65).

No significant difference in disease activity (a secondary outcome of the study), based on the Simple Clinical Colitis Index (SCCAI), was found between the web-based group and the control group at 12 months (OR 2.74, p = not significant). However, adherence to 4 weeks of acute treatment was increased by 31% in Denmark and 44% in Ireland compared to control
groups. Relapses in the web group were of shorter duration than in the control group: Denmark: median 18 days (95% CI 10 to 21) versus 77 days (95% CI 46 to 108 days), p<0.001, Ireland: median 30 days (95% CI 2-37 days) versus 70 days (95% CI 7-217 days), p<0.03. At the time of relapse, 100% of the Constant-care patients in Denmark started treatment with high dose 5-ASA compared to 10% of control patients, p<0.001. In Ireland only 15% of Constant-care patients started treatment with high dose oral 5-ASA compared to 10% of control patients.

Steroid use and hospitalisation were similar between the groups and there was no difference in adverse events due to 5-ASA treatment. In Denmark, both acute visits and routine visits were significantly reduced in the Constant-care group compared to the control group (21 vs 107 acute visits and 35 vs 92 routine visits, respectively, p<0.001). The financial saving to the department was €189 per patient per annum. Contact via email and phone were higher in the Constant-care group (107 vs 24 episodes of contact, respectively) (65).

In 2012, Constant-care was used to individualise infliximab dosing in patients with CD and this was found to be both feasible and safe (59). In 2014, Constant-care was then used to perform a prospective, open-labelled, web-guided study of 3 months of 5-ASA therapy for 95 patients with mild to moderately active UC (60). 86% of patients were adherent to web therapy, with a significant reduction in mean symptom scores (SCCAI 4.6 vs 1.6, p<0.001) and mean faecal calprotectin (437 vs 195 mcg/g, p<0.001) at week 0 and week 12 respectively. Almost 90% of patients decreased their dose of 5-ASA by week 12 of the study. Despite these promising results, Constant-care is not widely used even in Denmark, perhaps due to the amount of healthcare professional support needed to make it useful to patients.
1.2.2.2 UC HAT

A United States based home automated tele-management in patients with UC (UC HAT) trial randomised 47 patients to UC HAT (n=25) or usual care (n=22) for 12 months. UC HAT patients answered questions regarding disease activity, QoL, adherence, side effects and weight on a weekly basis. An educational curriculum was delivered after each session. Alerts and action plans were generated based on the results. Usual care was defined as routine follow-up, written action plans and educational fact sheets. There were no significant differences in disease activity or QoL between the two groups, and more than a third of patients withdrew from the study (51). Nevertheless, it is currently being assessed in a multi-centre randomised controlled trial (RCT) comparing standard of care to a telemedicine intervention that uses mobile phones and a secure provider portal to monitor symptoms, side effects, medications and weight on a weekly or fortnightly basis. This system sends personalised alerts and educational texts, and assesses symptoms and side effects. The primary analysis will compare change in disease activity and disease-specific QoL scores. A number of secondary outcomes will be compared among the groups, including health care utilisation, general QoL, patient knowledge and satisfaction (61).

1.2.2.3 HealthPROMISE

HealthPROMISE is a unique cloud-based patient-reported outcome and decision tool developed at the Sinai AppLab, Mount Sinai, New York. The app has been implemented at seven IBD centres and a single centre randomised controlled trial is currently in progress. The aim is to evaluate whether patient-centric self-monitoring combined with a collaborative decision making platform will improve QoL (measured by the Short Inflammatory Bowel Disease Questionnaire). For those randomised to HealthPromise (162/320), as opposed to an education app, data are entered every 2 weeks and these data are visible to the health provider through the electronic patient record. Both QoL and quality of care (QoC) (for example
surveillance colonoscopy, smoking cessation advice) have been incorporated into HealthPROMISE, allowing longitudinal measurements.

Baseline assessment showed that fatigue and tension (anxiety) were the two most important drivers of poor QoL. One year interim results showed that 75% of patients continued to login to the HealthPromise App. In a median follow up of 495 days, the proportion of patients meeting all eligible QoC parameters significantly increased in the intervention group vs the control group (28% vs 9%, p<0.01). Overall QoL started to improve among those randomised to HealthPROMISE within 5 months and was consistently above the control arm through a median of 495 days (62).

1.2.2.4 myIBDcoach

The Netherlands has developed myIBDcoach, a tele-medicine system for IBD patients, regardless of phenotype, severity or treatment (54, 63). It monitors disease activity, medication adherence, side effects, malnutrition, smoking, QoL, depression, stress, anxiety, life events, and work participation. It also provides e-learning opportunities. A randomised trial was performed in four hospitals. 909 patients were randomly assigned (1:1) to care via myIBDcoach (n=465) or standard care (n=444) and were followed up for 12 months. Patient using myIBDcoach were invited to visit the outpatient clinic at least once per year, or on demand. At 12 months, the mean number of outpatient clinic visits was lower in the myIBDCoach cohort (1.55, SD 1.50) than in the standard care cohort (2.34, SD 1.64; difference -0.79, 95% CI -0.98 to -0.59, p<0.0001). The mean number of hospital admissions was also decreased (0.05, SD 0.28 vs 0.10, SD 0.43; difference -0.05, 95% CI -0.01 to 0.00, p=0.046). There was no difference in QoL, mean number of flares, steroid use, emergency visits or need for surgery between the groups.
1.2.2.5 UCLA eIBD

Another IBD e-health technology has been developed at the UCLA Centre for IBD. This technology integrates patient reported outcome measures into electronic health records. This was launched in 2012 and can be found under “UCLA eIBD” in iTunes and Google Play stores however full functionality is only available to patients treated at the UCLA Centre for IBD. If a patient reaches a predefined symptom threshold, an automated message is sent to a nurse coordinator (66). A prospective randomised trial to assess the effect of this remote monitoring is planned.

1.2.2.6 IBD Qorus

IBD Qorus is the Crohn’s Colitis Foundation of America’s national initiative to improve quality of care for IBD patients (57, 58, 67). As part of this initiative, a patient-centred tool is being developed. This will incorporate symptom tracking, QoL, self-management, and shared decision making between patient and provider. It will also aim to facilitate communication during and between visits. It is proposed that when fully developed that the IBD Qorus technology platform will allow patients to look at their own data on a continuous basis. Only limited information regarding the development is available at this point in time.

1.2.3 TrueColours Bipolar Disorder

TrueColours UC is a bespoke adaptation of TrueColours Bipolar, a technology developed by the Oxford Department of Psychiatry. Bipolar disorder, also known as manic-depressive illness, is a disorder that causes unusual shifts in mood, energy, activity levels, and the ability to carry out day-to-day tasks. In bipolar disorder, short-term mood instability is pervasive and therefore regular monitoring is thought to represent a much more sensitive measure of outcome than, for example, counting the frequency of syndromal illness episodes.
TrueColours Bipolar was established over 10 years ago with the aim of tracking symptoms of mania and depression more accurately. It initially functioned via text messaging. Adherence to the text-messaging protocol was good at 75% over an average of 36 weeks, with 85% of responses obtained within 12 hours of a prompting message (68). The finding that SMS was readily adopted by the bipolar disorder population and that it resulted in findings matching other longitudinal studies (69, 70), led the psychiatry team, led by Professor Guy Goodwin and Professor John Geddes at the University of Oxford, to develop the technology. Over time, the TrueColours platform has become increasingly sophisticated and now works via email prompts.

This longitudinal, prospective data collection has allowed the psychiatry team to examine the proportion of time that patients spend in states of mania, depression, mixed-stage or euthymia and to evaluate subsequent time trends in the trajectory of symptoms. TrueColours Bipolar, via its ability for online mood tracking, has been used in psychoeducation studies (71). Until recently, most analyses of mood in bipolar disorder have been qualitative. TrueColours Bipolar, through providing detailed time series data, has allowed mathematical modelling of the course of bipolar disease (72).

Publications regarding TrueColours BPD are limited (68, 71, 73, 74) however it is currently being used in five clinical settings involving over 3000 patients:

- Oxford Health (adult) self-management system
- Oxford Health Child and Adolescent service
- Oxford Forensic Psychiatry Clinician led inpatient system
- Bipolar disorder research network
- Bipolar disorder research based in Canada (FLOURISH)
1.3 Aims and Outline of this thesis

1.3.1 Aims

The overall aim of this thesis was to create a programme to electronically collect and display personalised data for patients with ulcerative colitis. The potential benefit for both patients and the healthcare service were explored.

There are six themes addressed in this thesis which focus upon the potential of TrueColours UC. The aims are:

- To describe the process of adapting TrueColours Bipolar to TrueColours UC
- To assess the feasibility of TrueColours UC
- To assess the usability of TrueColours UC using a mixed-methods approach
- To assess patient perspectives on the impact of TrueColours UC using a qualitative approach
- To develop a prognostic clinical score to estimate the probability that an outpatient appointment will result in escalation of medical therapy in patients with known ulcerative colitis
- To analyse the longitudinal data created by real time data entry

1.3.2 Outline

The primary analysis of each of these aims are presented in Chapters 2 to 7. Within each chapter there is an introduction, methods, results and discussion. A summary of the findings and implications of this thesis are presented in Chapter 8. References and appendices are presented at the end of the thesis.
2 Chapter Two

Adaptation of TrueColours Bipolar Disease to TrueColours Ulcerative Colitis

2.1 Introduction

TrueColours is a bespoke web-based software platform developed by the Department of Psychiatry, University of Oxford, UK. TrueColours Bipolar is established across a range of mental health cohorts (child, adolescent, forensic, and adult (74)) in both clinical and research capacities. A logical development was to assess its value for other chronic diseases, such as IBD. Adaptation from one disease to another requires careful consideration about what data to collect. Consequently, it was decided first to adapt TrueColours to UC and not to CD. This was because UC has more clearly defined clinical, endoscopic, histopathological and biomarker disease activity indices (75).

For UC, components related to disease activity assessment include clinical symptoms, quality of life (QoL), endoscopy, histopathology and biomarkers. The importance of each of these is detailed below. A comprehensive system would need to also collect demographic data, medication, and outcomes such as anaemia, emergency department presentations, need for hospitalisation and complications of any interventions.

Symptoms and response to medical therapy are crucial to the management of UC. Conventional management focuses on assessment during brief outpatient clinic visits sometimes weeks or months apart. Symptoms may wax and wane in the intervening period. Treatment decisions in clinic are often reactive, based on subjective patient recall of their
symptoms; therefore the ability to record these symptoms in real-time would improve accuracy. Likewise, QoL is important in the assessment of UC because it evaluates social and emotional well-being and patient perspective which are important components of medical decision making (76).

Endoscopic evaluation is equally as important because mucosal healing is recognised as a therapeutic goal for UC and is increasingly being used in clinical practice to guide decision making (77). Mucosal healing has been associated with a decreased need for corticosteroids (78), decreased hospitalisation rates (79-81), sustained clinical remission (82), decreased colectomy (78, 79, 81, 82) and decreased risk of colorectal cancer (83).

Microscopic inflammation can persist despite the appearance of endoscopically healed colonic mucosa, representing residual disease activity (84, 85). Observational studies have shown that persistent histological inflammation in UC is associated with an increased risk of relapse, hospitalisation, colectomy and colorectal cancer (85-87). Histological remission is not yet recommended as a treatment target in clinical trials or practice (75), but this appears likely to change.

Biomarkers help to assess disease activity in UC (75). Faecal calprotectin is a protein that is present in the faeces when intestinal inflammation is present. Testing the calprotectin levels is thereby a non-invasive tool for monitoring disease activity. It has been shown to predict persistent inflammation (88-90), risk of relapse (91-94), and is responsive to up-titration of therapy (95). The clinical utility of faecal calprotectin levels for an individual patient lies in monitoring the change of this biomarker over time, with rising levels prompting endoscopic evaluation or change in therapy (96).
As well as the above components to assess disease activity, it is also important that outcome data are collected. The International Consortium of Health Outcomes Measurement (ICHOM) has defined global Standard Sets of outcome measures for many different diseases. A Standard Set is a group of items focused on disease-specific outcomes that matter most to patients. An international, multidisciplinary IBD working group (n=25) from 12 countries defined a Standard Set for collection in IBD. Outcome domains include patient-reported outcome measurements, survival and disease control, treatment-related complications, and healthcare utilisation, to be measured at baseline and at 6 or 12 month intervals (97). This Standard Set provided a template for collecting these measures of treatment outcomes in TrueColours UC.

Inclusion of treatment guidance was considered. The European Crohn’s and Colitis Organisation (ECCO) guidelines recommend 5-ASA therapy for patients with UC (10). Treatment guidance for 5-ASA and topical therapies has been successfully trialled in another web-based UC programme, Constant-care. For patients with mild to moderately active UC, acute treatment with 4g daily of 5-ASA plus/minus topical rectal treatment was recommended based on clinical symptoms indicating a flare of disease. When a patient entered remission, a maintenance dose was then recommended. Patients were encouraged to contact their IBD unit if symptoms were worsening. No advice regarding oral prednisolone, immunosuppressant or biologic use was given. Not only did 88% of web-based patients prefer this approach but self-initiation of oral 5-ASA therapy did not lead to an increase in adverse events or hospital referred serious adverse events. The relapse time by reduced by 59 days in the web-based group (65). This established a basis for treatment guidance in TrueColours UC.
The aim of this chapter is to describe the adaptation from TrueColours Bipolar to TrueColours UC. To do this, disease-specific symptom, QoL and outcome questionnaires were selected. To enable a holistic overview of disease activity, several new features were added to the TrueColours UC platform: faecal calprotectin, entry of blood, endoscopy and histopathology results, colour coding for different thresholds of disease activity, a medication timeline and personalised treatment guidance.

Description of the adaptation process does not naturally fit with the normal structure of methods and results sections. However, to achieve uniformity throughout this thesis, the approach for each feature of TrueColours UC is described first in the methods section with the outcome or selections explained in the results sections. Following the adaptation, a pre-pilot was conducted. This was done to ensure that no major technical or usability problems were present prior to the commencement of the 6 month pilot. This pre-pilot information is also included in the methods and results sections.
2.2 Methods

2.2.1 TrueColours UC website

The TrueColours UC website was based upon the TrueColours Bipolar website:


2.2.2 TrueColours UC security

TrueColours UC security was based upon the security parameters of TrueColours Bipolar which sits on a secure NHS server. All accounts within the TrueColours programme are username and password protected. A patient can only view their own account however a physician or nursing staff can see all of their patients’ accounts.

2.2.3 TrueColours UC registration and email prompts

TrueColours UC registration was based on TrueColours Bipolar registration. For a patient to be registered, the patient needs to be “set-up” by a physician or nurse or administrator by entering patient name, date of birth, email address, and other contact details. For TrueColours to be able to send its email prompts, the person registering the patient needs to choose the questionnaires along with start date, desired frequency of the email prompts (daily to 3 monthly) and a stop date. Once the schedule is finalised, emails are sent to the patient automatically. These emails contain a direct link to the questionnaires scheduled for that day.

In TrueColours Bipolar, disease-specific questionnaires (Quick Inventory of Depressive Symptoms – Self Report (QIDS-SR) (98) and the Altman Self-Rating Mania scale (ASRM) (99)) are sent on a weekly basis. The patient is then able to complete these questionnaires electronically, and once submitted, the scores are logged on a graph allowing monitoring of their mood scores over time (Figure 2-1).
2.2.4 Demographic data

Demographic data fields were determined by the existing Oxford IBD Cohort database, a prospective database containing over 3300 IBD patients. Additionally, given that TrueColours UC is a web-based programme, the amount of internet and social media use was considered relevant. A demographic questionnaire to be integrated into TrueColours UC was drafted (AW) and reviewed (two gastroenterology physicians and five UC patients) to assess readability.

2.2.5 Disease-specific activity indices

TrueColours UC established separate entries for each domain of disease activity assessment, using independently validated indices (96). The literature was reviewed within each domain: clinical symptoms, quality of life, endoscopic appearance, histopathology and biomarkers. Bibliographic searches were performed of online databases (OVID SP MEDLINE, OVID EMBASE, National Pubmed Central Medline, Cochrane Library, conference abstracts), using the medical subject heading (MeSH) terms and key words set out below.
Clinical disease activity indices

(“inflammatory bowel disease” OR “ulcerative colitis” or “colitis”) AND
(“activity” OR “indices” OR “index” OR “activity indices”)

Quality of Life

(“inflammatory bowel diseases” OR “ulcerative colitis” OR “colitis”) AND
(“quality of life”) OR (“questionnaire”)

Endoscopic disease activity indices

(“inflammatory bowel disease” OR “ulcerative colitis” or “colitis”) AND
(“endoscopy” OR “endoscopic” OR “mucosal healing” OR “endoscopic scoring”)

Histological disease activity indices

(“inflammatory bowel diseases” OR “ulcerative colitis” OR “colitis”) AND
(“histology” OR ”histological healing” OR “pathological healing” OR histological scoring” OR pathological scoring”)

Calprotectin

(“inflammatory bowel diseases” OR “ulcerative colitis” OR “colitis”) AND
(“calprotectin”)

Free text variations of these terms were also used. A hand-search of article bibliographies was undertaken. Articles were limited to those in English and pertaining to human subjects. All included articles were screened by AW. Studies were included if they described an index for disease activity assessment in UC. Composite indices (for example, indices that required both symptoms and endoscopy) were excluded. Table 2-1 lists the indices that were considered for TrueColours UC. Selection of the indices for each domain was based on: extent of validation; responsiveness and experience in clinical trials; international expert opinion (75); active comparison between all indices in clinical practice (100); and perceived ease of use within TrueColours UC.
Table 2-1: List of non-composite disease activity indices for ulcerative colitis

<table>
<thead>
<tr>
<th>Type of Index</th>
<th>Index Main Name</th>
<th>Abbreviation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Partial Mayo Score</td>
<td></td>
<td>(101, 102)</td>
</tr>
<tr>
<td></td>
<td>Simple Clinical Colitis Activity Index</td>
<td>SCAI</td>
<td>(103)</td>
</tr>
<tr>
<td></td>
<td>Modified Truelove &amp; Witts’ index</td>
<td>MTWSI; Lichtiger score</td>
<td>(104)</td>
</tr>
<tr>
<td></td>
<td>Ulcerative Colitis Clinical Score</td>
<td>UCCS</td>
<td>(105)</td>
</tr>
<tr>
<td></td>
<td>Physician Global assessment</td>
<td>PGA</td>
<td>(106)</td>
</tr>
<tr>
<td></td>
<td>Investigators Global Evaluation</td>
<td></td>
<td>(107)</td>
</tr>
<tr>
<td></td>
<td>Paediatric Ulcerative Colitis Activity Index</td>
<td>PUCAI</td>
<td>(108)</td>
</tr>
<tr>
<td></td>
<td>Beattie Paediatric Ulcerative Colitis Index</td>
<td></td>
<td>(109)</td>
</tr>
<tr>
<td>Quality of Life</td>
<td>Inflammatory Bowel Disease Questionnaire</td>
<td>IBDQ</td>
<td>(110)</td>
</tr>
<tr>
<td></td>
<td>IBD-Control Questionnaire</td>
<td>IBD-Control</td>
<td>(111)</td>
</tr>
<tr>
<td></td>
<td>Short inflammatory Bowel Disease Questionnaire</td>
<td>S-IBDQ</td>
<td>(112)</td>
</tr>
<tr>
<td></td>
<td>Crohn’s ulcerative Colitis Quality-8</td>
<td>CUCQ-8</td>
<td>(113)</td>
</tr>
<tr>
<td></td>
<td>Rating form of IBD Patient Concerns</td>
<td></td>
<td>(114)</td>
</tr>
<tr>
<td></td>
<td>UK-Inflammatory Bowel Disease Questionnaire</td>
<td></td>
<td>(115)</td>
</tr>
<tr>
<td>Endoscopy</td>
<td>Rachmilewitz endoscopic index</td>
<td></td>
<td>(116)</td>
</tr>
<tr>
<td></td>
<td>Baron score</td>
<td>Baron</td>
<td>(117)</td>
</tr>
<tr>
<td></td>
<td>Truelove and Witts’ endoscopy index</td>
<td></td>
<td>(33)</td>
</tr>
<tr>
<td></td>
<td>Powell-Tuck sigmoidoscopic index</td>
<td></td>
<td>(118)</td>
</tr>
<tr>
<td></td>
<td>Sutherland endoscopic index</td>
<td></td>
<td>(119)</td>
</tr>
<tr>
<td></td>
<td>Modified Baron index</td>
<td></td>
<td>(105)</td>
</tr>
<tr>
<td></td>
<td>Mayo clinic index: Endoscopic subscore</td>
<td>Mayo endoscopy score</td>
<td>(102)</td>
</tr>
<tr>
<td></td>
<td>Rachmilewitz endoscopic index</td>
<td></td>
<td>(116)</td>
</tr>
<tr>
<td></td>
<td>Endoscopy Activity index</td>
<td>EAI</td>
<td>(120)</td>
</tr>
<tr>
<td></td>
<td>Ulcerative Colitis Endoscopic index of Severity</td>
<td>UCEIS</td>
<td>(121, 122)</td>
</tr>
<tr>
<td></td>
<td>Matts index</td>
<td></td>
<td>(123)</td>
</tr>
<tr>
<td>Histopathology</td>
<td>Watts Score</td>
<td>(116)</td>
<td></td>
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<td>----------------</td>
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<td></td>
</tr>
<tr>
<td>Matts Score</td>
<td></td>
<td>(124)</td>
<td></td>
</tr>
<tr>
<td>Friedman Index</td>
<td></td>
<td>(125)</td>
<td></td>
</tr>
<tr>
<td>Powell-Tuck Score</td>
<td></td>
<td>(123)</td>
<td></td>
</tr>
<tr>
<td>Korelitz Index</td>
<td></td>
<td>(120)</td>
<td></td>
</tr>
<tr>
<td>Truelove and Richards Index</td>
<td></td>
<td>(115)</td>
<td></td>
</tr>
<tr>
<td>Keren Score</td>
<td></td>
<td>(121, 122)</td>
<td></td>
</tr>
<tr>
<td>Gomes Score</td>
<td></td>
<td>(123)</td>
<td></td>
</tr>
<tr>
<td>Saverymutti Index</td>
<td></td>
<td>(126)</td>
<td></td>
</tr>
<tr>
<td>Floren Index</td>
<td></td>
<td>(127)</td>
<td></td>
</tr>
<tr>
<td>Initial Riley Score</td>
<td></td>
<td>(118)</td>
<td></td>
</tr>
<tr>
<td>Riley Score</td>
<td></td>
<td>(128)</td>
<td></td>
</tr>
<tr>
<td>Scheppach Score</td>
<td></td>
<td>(129)</td>
<td></td>
</tr>
<tr>
<td>Hanauer Score</td>
<td></td>
<td>(130)</td>
<td></td>
</tr>
<tr>
<td>Odze Score</td>
<td></td>
<td>(131)</td>
<td></td>
</tr>
<tr>
<td>Sandborn Score</td>
<td></td>
<td>(132)</td>
<td></td>
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<tr>
<td>Geboes Score</td>
<td></td>
<td>(133)</td>
<td></td>
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<tr>
<td>Harpaz Score</td>
<td></td>
<td>(134)</td>
<td></td>
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<tr>
<td>Rutter Score</td>
<td></td>
<td>(135)</td>
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<tr>
<td>Modified Riley Score</td>
<td></td>
<td>(106)</td>
<td></td>
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<tr>
<td>The Chicago Score</td>
<td></td>
<td>(136)</td>
<td></td>
</tr>
<tr>
<td>Gupta Index</td>
<td></td>
<td>(137)</td>
<td></td>
</tr>
<tr>
<td>Gramlich Index</td>
<td></td>
<td>(138)</td>
<td></td>
</tr>
<tr>
<td>Baars Score</td>
<td></td>
<td>(139)</td>
<td></td>
</tr>
<tr>
<td>The Nancy Histological Index</td>
<td>Nancy Index</td>
<td>(83)</td>
<td></td>
</tr>
<tr>
<td>Robarts Histopathology Index</td>
<td>RHI</td>
<td>(105)</td>
<td></td>
</tr>
</tbody>
</table>
2.2.6 *Generic Quality of Life Questionnaire*

To enable benchmarking against other chronic diseases, a generic QoL measure was needed. The European Quality of Life – 5 Dimensions (EQ-5D) is a standardised instrument that is used as a measure of health outcomes. It is applicable to a wide range of health conditions and provides a descriptive profile and a single value for health status. It was primarily designed for self-completion, taking only a few minutes to complete (140). Since 2009, the National Health Service PROMs programme has collected EQ-5D data pre- and post-surgery for hip and knee surgery, hernia repair and varicose veins (141).

2.2.7 *International Consortium of Health Outcomes Management (ICHOM)*

The ICHOM Standard Set for IBD was reviewed to identify items not captured by other TrueColours UC questionnaires. Although this was not the initial aim of TrueColours UC, collection of these data was thought to be feasible. Questions to be used were drafted (AW and ST) and reviewed by five UC patients to assess readability.

2.2.8 *Personalised questions*

Options for personalised questions relevant to UC disease activity were drafted (AW) and reviewed by the same five UC patients. Patients requested an option to create their own questions, which was included.

2.2.9 *Frequency of questionnaires*

There is no validated frequency for collecting questionnaires in real time monitoring programmes. A balance must be struck between the amount of information collected and user fatigue and burden. However, since a focus of TrueColours UC was to examine fluctuations in disease activity, the frequency of each questionnaire aimed to maximise data collection.
For the TrueColours UC 6 month pilot, the frequency of individual questionnaire email prompts needed to be uniform for all patients.

2.2.10 Evaluation of patients completing the Simple Clinical Colitis Activity Index

The SCCAI was originally developed to be used by physicians rather than patients (103). Walmsley (142), the creator of the SCCAI, later showed good correlation between patients and physicians completing the original SCCAI. A Dutch group developed a patient-based SCCAI (p-SCCAI) whereby the original SCCAI was translated into lay language with all medical terminology clarified. The p-SCCAI correlated well with physicians completing the SCCAI (Spearman’s correlation coefficient = 0.79) (143). The p-SCCAI however, has not been validated.

A decision about whether to use the original SCCAI or the p-SCCAI needed to be made. In earlier work, the author of this thesis (AW), examined inter-observer variation among commonly used UC indices (100). An unpublished component of this work was the patient–physician inter-observer variation using the original SCCAI. 100 UC patients were seen by four consecutive physicians, in random order. Prior to the consultation, each patient completed a questionnaire that included 5 of the 6 SCCAI questions, excluding those on extraintestinal manifestations. Each physician completed the original SCCAI after seeing the patient. Agreement between a patient and the four physicians was assessed using (weighted) Kappa statistic of agreement. The weighted kappa considers the degree of disagreement between the two raters. Kappa values are interpreted as: <0.2 poor; 0.21 to 0.4 fair; 0.41 to 0.6 moderate; 0.61 to 0.80 good and 0.81 to 1.0 very good agreement (144). The average
agreement between the patient and each physician was used as the overall agreement and results are reported in this thesis.

2.2.11 Thresholds for SCCAI

Thresholds for the SCCAI (range 0-19) were determined from previous publications (145-147): remission (0-2), mild (3-5), moderate (6-11) and severe (12-19). Colour coding was applied to these thresholds.

2.2.12 Conversion from paper to electronic versions

The electronic format of each questionnaire was intended to replicate its paper version. For each questionnaire, a paper version (Microsoft Word document) with instructions was given to the TrueColours development team who then programmed the questionnaire into the TrueColours UC platform. Following testing in a local environment, the software was deployed to a testing website for review by AW. Any necessary changes were made and once approved, the questionnaire was uploaded to the live TrueColours UC site.

2.2.13 Electronic patient-reported outcome measure (ePROM) validity

An electronic PROM (ePROM) is a PROM that is collected by electronic methods. Two meta-analyses have concluded that PROMs administered on paper are quantitatively comparable with measures administered on an electronic device (148, 149). Despite this, the International Society for Pharmacoeconomics and Outcome Research (ISPOR) ePRO Task Force recommends that when an ePROM version is created, evidence should demonstrate that the measurement properties of the ePROM are comparable to the original paper version (39).
Comparability of an ePROM is governed by the amount of content modification during migration from paper to digital format. For TrueColours UC, there were some formatting changes (e.g., one question per screen, rather than multiple items per page), but no changes to the content or meaning of the questions. Modifications were therefore classified as minor (39), so in accordance with ISPOR recommendations, cognitive debriefing and usability testing were performed.

Cognitive debriefing involved assessment of several ePROMs (SCCAI, IBD Control-8 and CUCQ-8) used in TrueColours UC to assess whether the ePROM application changed the way patients interpreted the questions, decided on an answer and responded. During cognitive debriefing interviews, patients filled out the questionnaires on a laptop while being observed by AW. Each question and item were discussed to judge interpretation and ease of choosing the correct response. Cognitive debriefing interviews were audio-recorded and transcribed verbatim by a professional transcriber. NVivo 11 software was used to enter the results for each question to assist the analysis of the interpretations. Usability testing is described in Chapter 4.

2.2.14 Faecal calprotectin

The IBDoc® faecal calprotectin (FCal) test kit, produced by Buhlmann Laboratories, is a pre-pakaged kit that provides the equipment and instructions to allow patients to test their own stool in the privacy of their own home. A series of steps is required to transfer some stool to a test “cassette”. The accompanying software (CalApp®, available for iOS and Android) turns the smartphone into a test cassette reader. By scanning the cassette it calculates a quantitative calprotectin concentration (see Appendix A). Results are then transferred to a clinician-facing
web portal, the IBDoc® Portal and its associated application processing interface (API). An API is a list of formatted commands allowing individual programmes to communicate with one another directly.

Normally, physicians would view the FCal results on the IBDoc® Portal. To achieve graphic representation of FCal in TrueColours UC, communication between IBDoc® and TrueColours UC was required. This communication was developed by the TrueColours software team. At patient registration, TrueColours UC communicated with the IBDoc® API to create a patient file in the IBDoc® Portal which then linked back to the TrueColours UC patient file. Daily secure requests were made from the TrueColours UC server to the IBDoc® Portal to update results.

2.2.15 Pathology results

Pathology results and research sample documentation were not previously part of the TrueColours platform. A list of blood, endoscopy and histopathology results for entry into TrueColours UC was drafted by AW. The TrueColours software team created a mechanism whereby all results could be entered manually, since the work to link TrueColours UC to the hospital electronic patient record was deemed inappropriate at this pilot stage.

2.2.16 Medications

Categories of medication (topical treatments, 5-ASA agents, steroid therapy, biologic or other) were integrated into TrueColours UC. A list of medications within each category as well as the appropriate dose ranges were added. Baseline medication (including dose and
frequency) was entered at the time of registration and could be adjusted by either the patient or the TrueColours UC research team.

2.2.17 Treatment guidance

Consideration was given to the appropriateness and safety of treatment guidance. Awareness of the legal implications led to a caveat clause and warning, emphasising that the advice only represented guidance and the need to discuss with a healthcare professional in the event of deterioration or severe symptoms. Advice would be restricted to oral 5-ASA agents and topical rectal medications. Treatment guidance was linked to clinical disease activity (refer to SCCAI thresholds 2.2.11). Multiple iterations of the templates (AW and ST) were needed to achieve satisfactory phrasing that gave guidance rather than being prescriptive. Templates for each level of disease activity were incorporated into the TrueColours UC platform by the software team. All guidance was individualised at the time of registration in the pilot. This guidance then appeared alongside the daily SCCAI score.

2.2.18 Design of TrueColours UC

Design elements were undertaken by a web and software development company, ‘White October’ (150). Sample designs were piloted with two physicians, three nursing staff and five UC patients. Layout and functionality of the digital pages were reviewed by AW and the TrueColours software team.

2.2.19 Pre-pilot

For the pre-pilot, UC patients were recruited from the IBD Clinic at the John Radcliffe Hospital. Patients were asked to use TrueColours UC for three weeks. No FCaI, blood tests or endoscopic procedures were required for this pre-pilot. Patients were registered on the TrueColours UC live site. After three weeks of receiving email prompts, quantitative
assessment of usability using the System Usability Scale (SUS) (see Chapter 4, section 4.2.1.2, page 79) was performed. Verbal and email feedback was also encouraged.

2.3 Results

2.3.1 TrueColours UC website

A website address was established: https://ouh.truecolours.nhs.uk/ibd/en/

2.3.2 TrueColours UC security

It was arranged that the TrueColours UC data would sit alongside the TrueColours Bipolar data on the dedicated NHS server. All accounts were formatted as per standard procedure in TrueColours Bipolar including being username and password blocked.

2.3.3 TrueColours UC registration and email prompts

No changes to the process of registration or email prompting were required.

2.3.4 Overview of Adaptation

Following the adaptation, Truecolours UC provided real time monitoring via electronic questionnaires sent via email. The TrueColours platform allowed multiple questionnaires along with the corresponding frequency of email prompts to be selected by the research team. Although questionnaires are the basis for TrueColours monitoring, TrueColours UC was adapted to enable a more holistic picture of disease activity. Additional features included FCal monitoring, external data entry of laboratory and endoscopic results, medication and personalised treatment guidance (Table 2-2). Each of the following result sub-sections will describe the outcome of each feature of TrueColours UC.
Table 2-2: Features of TrueColours UC

<table>
<thead>
<tr>
<th>Existing features adapted for TrueColours UC</th>
<th>New features designed for TrueColours UC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Questionnaires</td>
<td>Integration of IBDx® faecal calprotectin</td>
</tr>
<tr>
<td>Demographic</td>
<td>Entry of external results</td>
</tr>
<tr>
<td>Symptom: SCCAI</td>
<td>Bloods</td>
</tr>
<tr>
<td>QoL: IBD Control-8, CUCQ-8, EQ-5D-3L</td>
<td>Endoscopy</td>
</tr>
<tr>
<td>ICHOM parameters</td>
<td>Histopathology</td>
</tr>
<tr>
<td>Personalised questionnaires</td>
<td>Treatment Guidance</td>
</tr>
<tr>
<td>Flexibility for frequency of questionnaires</td>
<td></td>
</tr>
<tr>
<td>Medication</td>
<td></td>
</tr>
</tbody>
</table>

QoL=Quality of Life, IBD Control-8=IBD Control-8 items, CUCQ-8=Crohn’s Ulcerative Colitis Questionnaire-8 items, ICHOM=International Consortium for Health Outcomes Measurement

2.3.5 Demographics

The questionnaire for baseline demographics was integrated into TrueColours UC. Date of birth, gender, weight (kg), height (cm), date of UC diagnosis (month/year), worst ever extent of disease (guided by the Montreal classification: E1, E2, E3) (151), level of education (none, primary, secondary, tertiary), smoking status (never, ex-smoker or current smoker), presence of extraintestinal manifestations (pyoderma gangrenosum, erythema nodosum, uveitis and inflammatory arthritis, liver or bile duct disease), access to WiFi at home, time spent on the internet each day (hours), and use of social media.

2.3.6 Indices chosen

2.3.6.1 Clinical index – the SCCAI

Of the eight pure symptom indices in Table 2-1, one needed to be selected. The SCCAI (103) (See Appendix B) was chosen because it includes symptoms of importance to patients that other indices do not (nocturnal bowel movements and urgency of defaecation) and does not require a physician’s global assessment. The SCCAI has been prospectively compared with multiple other UC indices and along with the Paediatric Ulcerative Colitis Activity Index.
(PUCAI) (108), it performed best of all non-invasive indices for validity, reliability, responsiveness and feasibility. The SCCAI also sufficiently discriminated remission from active disease (148, 152). TrueColours UC was not designed to manage acute severe ulcerative colitis (ASUC) so did not monitor criteria relevant to ASUC.

### 2.3.6.2 Quality of Life indices – IBD Control, CUCQ-8 and EQ-5D

Most disease-specific QoL indices for IBD are lengthy and time-consuming (39), which precludes their routine use. Two disease-specific QoL indices were chosen for TrueColours UC, the IBD Control-8 (111) and the Crohn’s Ulcerative Colitis Questionnaire-8 (CUCQ-8) (113). The rationale for choosing these two questionnaires is outlined below.

IBD Control (See Appendix C) uses generic terms applicable both to UC and CD and is the first patient-reported outcome measure to capture disease control from the patient’s perspective. It is fast to complete, internally reliable, reproducible, responsive and acceptable to patients. Validity has been tested against more complex QoL questionnaires, disease activity assessment and Physician Global Assessment (111). A limited version, IBD Control-8, includes 8 of the 14 questions, with scores ranging from 0 (worst) to 16 (best). IBD Control is free to use and (unlike some QoL indices) not subject to licence. IBD Control has been adopted by ICHOM (97) and the UK IBD Registry (http://ibdregistry.org.uk), although has not yet been used in clinical trials.

The CUCQ-8 (a short version of the CUCQ-32) (See Appendix D) has been validated in 205 patients, designed for use in clinical practice. It has eight questions, each out of 1, with total scores ranging from 0 (best) to 8 (worst) QoL, which is the other way around to the IBD-Control. The CUCQ-8 is also free to use, is not subject to licence and has been used as the primary end-point in a randomised clinical trial (CONSTRUCT) in UC (153).
The EQ-5D (140) was included in TrueColours UC. It comprises the following five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Although the 5-level version of the EQ-5D (EQ-5D-5L) is being increasingly used, the 3-level version (EQ-5D-3L) was chosen for TrueColours UC due to the logistics of smartphone screen design (3 levels enabled the entire question and answers to fit on a single screen). For EQ-5D-3L, each dimension has three levels: no problems, some problems, extreme problems. Use of the EQ-5D-3L was registered with the EuroQol Research Foundation. The EQ-5D-3L was scored using the UK time trade off (TTO) value set code (ranging from 0 (worst) to 1 (best)). The EQ-5D visual analogue scale (VAS) records self-rated health status where 0 is labelled “worst imaginable” and 100 is labelled “best imaginable” health state.

2.3.6.3 Endoscopic Index -UCEIS

The UCEIS is the only validated endoscopic index for UC (121) (See Appendix E). The endoscopist grades vascular pattern, bleeding and erosions or ulcerations according to defined criteria, leading to a score from 0 (normal) to 8 (worst ever colitis). Disadvantages of the UCEIS include that the extent of disease is not documented (as only the worst affected area is scored) and there are no validated thresholds for mild, moderate, or severe disease. The UCEIS accounts for 88% of inter-observer variation (121, 154), and correlated closely (r=0.92) with the validated histopathology Nancy index (155).

2.3.6.4 Histopathology Index - Nancy index

There are 26 histological activity indices in UC, only two of which are validated, the Nancy Index (156) and the Robarts Histopathology Index (RHI) (157). The Nancy Index was chosen for TrueColours UC because it is simple (scale 0-4), reproducible and responsive (See Appendix F).
2.3.6.5 ICHOM parameters

The ICHOM IBD Standard Set outcome metrics (excluding IBD Control-8 which was already included in TrueColours UC) were included in TrueColours UC: weight, prednisolone use, complications due to IBD interventions, outcome of complications, number of emergency department visits, number of hospital admissions and length of stay (days), diagnosis of bowel cancer and if so whether in a surveillance programme at the time, previous diagnosis of Hepatitis B, Hepatitis C or HIV.

2.3.6.6 Personalised Questions

Personalised questionnaires were available to all patients on a daily or weekly basis, to allow patients to document factors that might have an impact on their disease or QoL (Table 2-3). Pre-made categories and options were available or patients could formulate their own questions. Yes, no or numerical answers were required (in order to be able to present these results graphically). A maximum of 10 daily and 10 weekly questionnaires per patient were permitted. These results were then graphed below the symptom and QoL graphs.

Table 2-3: Personalised questionnaire categories and options in TrueColours UC

<table>
<thead>
<tr>
<th>Categories</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>On a scale of 1 to 100 (1 being no pain and 100 being the worst pain imaginable), how is your pain today?</td>
</tr>
<tr>
<td>Activity level</td>
<td>Yesterday, how many minutes of exercise did you do?</td>
</tr>
<tr>
<td></td>
<td>Yesterday, how active were you? (0 is not active at all and 10 is as active as you could be)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Yesterday, how many alcoholic drinks did you have?</td>
</tr>
<tr>
<td>Dietary triggers</td>
<td>Food intake appears to trigger my symptoms (Yes/No).</td>
</tr>
<tr>
<td></td>
<td>I ate well yesterday (Yes/No).</td>
</tr>
<tr>
<td>Adherence to medication</td>
<td>I took my medications yesterday (Yes/No)</td>
</tr>
<tr>
<td></td>
<td>I took my medications last night (Yes/No)</td>
</tr>
<tr>
<td></td>
<td>I took my medications this morning (Yes/No)</td>
</tr>
</tbody>
</table>
2.3.7 Frequency of questionnaires

Decided upon questionnaire frequencies are displayed in Table 2-4. To examine fluctuation in disease symptoms, the SCCAI was administered daily. The SCCAI was originally designed for use every three days (103), although other studies have used it every seven days for stable patients (143). The IBD Control-8 and CUCQ-8 measure quality of life over the preceding two weeks, so it was decided to administer these fortnightly. ICHOM generally recommend 6-12 monthly data collection, but this interval was modified to three to four months for this pilot.

Table 2-4: Frequency of questionnaires in TrueColours UC

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td>Baseline (within 1 month)</td>
</tr>
<tr>
<td>Symptom - SCCAI</td>
<td>Daily</td>
</tr>
<tr>
<td>QoL – IBD Control 8, CUCQ8 and EQ-5D-3L</td>
<td>Fortnightly</td>
</tr>
<tr>
<td>ICHOM parameters</td>
<td>Baseline (within 1 month) and 4 months</td>
</tr>
<tr>
<td>Personalised</td>
<td>Daily or weekly as per patient preference</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index
2.3.8 Patient-Physician inter-observer variation for the SCCAI

There was good to very good agreement between patients and physicians for the five tested components of the SCCAI (Table 2-5).

Table 2-5: Agreement between patient and physician SCCAI scores

<table>
<thead>
<tr>
<th>Descriptors</th>
<th>Physician 1 weighted Kappa (95% CI)</th>
<th>Physician 2 weighted Kappa (95% CI)</th>
<th>Physician 3 weighted Kappa (95% CI)</th>
<th>Physician 4 weighted Kappa (95% CI)</th>
<th>Average weighted Kappa*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel frequency day</td>
<td>0.91 (0.85-0.95)</td>
<td>0.89 (0.80-0.95)</td>
<td>0.84 (0.73-0.91)</td>
<td>0.85 (0.76-0.92)</td>
<td>0.87</td>
</tr>
<tr>
<td>Bowel frequency night</td>
<td>0.85 (0.71-0.94)</td>
<td>0.80 (0.67-0.90)</td>
<td>0.80 (0.64-0.89)</td>
<td>0.72 (0.56-0.83)</td>
<td>0.79</td>
</tr>
<tr>
<td>Urgency of defecation</td>
<td>0.80 (0.63-0.88)</td>
<td>0.80 (0.67-0.89)</td>
<td>0.76 (0.60-0.87)</td>
<td>0.70 (0.56-0.81)</td>
<td>0.76</td>
</tr>
<tr>
<td>Blood in stool</td>
<td>0.90 (0.80-0.94)</td>
<td>0.94 (0.90-0.96)</td>
<td>0.93 (0.89-0.96)</td>
<td>0.86 (0.80-0.92)</td>
<td>0.91</td>
</tr>
<tr>
<td>General well-being</td>
<td>0.90 (0.80-0.95)</td>
<td>0.90 (0.81-0.96)</td>
<td>0.93 (0.85-0.97)</td>
<td>0.90 (0.82-0.95)</td>
<td>0.91</td>
</tr>
</tbody>
</table>

*Kappa values are interpreted as: <0.2 poor; 0.21 to 0.4 fair; 0.41 to 0.6 moderate; 0.61-0.8 good and 0.81 to 1.0 very good agreement.
2.3.9 Thresholds

Thresholds for SCCAI and colour assigned for TrueColours UC are displayed in Table 2-6.

Table 2-6: SCCAI thresholds and colour coding for TrueColours UC

<table>
<thead>
<tr>
<th>SCCAI total score</th>
<th>Category assigned</th>
<th>Colour assigned</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2</td>
<td>Remission</td>
<td>Dark green</td>
</tr>
<tr>
<td>3 to 5</td>
<td>Mild</td>
<td>Light green</td>
</tr>
<tr>
<td>6 to 11</td>
<td>Moderate</td>
<td>Amber</td>
</tr>
<tr>
<td>≥ 12</td>
<td>Severe</td>
<td>Red</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index

When a SCCAI questionnaire was submitted, the total score was calculated (0 to 19). This score was displayed with:

1. The corresponding colour (dark green, light green, amber or red)
2. An indicator of where that score fits on the SCCAI scale
3. A ‘smiley’ face (Figure 2-2)

Figure 2-2: An example of an SCCAI score of 7 with corresponding guidance
The above thresholds and colours were also used as the background colours for the SCCAI symptom graph, allowing patients to more easily track their symptoms over time (Figure 2-3).

**Figure 2-3: An example of a medication timeline and graphs**

(A) Medication timeline and SCCAI colour coded symptom graph

(B) IBD Control - 8 graph

(C) IBDoc® faecal calprotection
2.3.10 ePROM validity

A review of the draft electronic versions of the questionnaires led to minor changes in format. Examples included ensuring that question order and language were consistent with the paper version.

Cognitive debriefing for the SCCAI, IBD Control-8 and CUCQ-8 was conducted with five patients. This confirmed that despite minor modifications in format, patient understanding of all three questionnaires was unchanged by administering the questionnaires in electronic format (for usability results, see Chapter 4). Cognitive debriefing revealed that further explanation of the original SCCAI may be required for patients for both paper and electronic versions, as suggested by Bennebroek et al (143). An example of cognitive debriefing results is shown in Table 2-7.

Table 2-7: Cognitive debriefing results for Descriptor 2 of the SCCAI

<table>
<thead>
<tr>
<th>SCCAI descriptor wording</th>
<th>Patient Response to Question “Do you understand what this means?”</th>
<th>Patient interpretation of the question</th>
<th>Investigator’s comments and suggested changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 2 Bowel frequency (nocturnal)</td>
<td>Patient 1- Yes</td>
<td>If I had to get out of bed at night time.</td>
<td>Interpretation was good</td>
</tr>
<tr>
<td></td>
<td>Patient 2- Yes</td>
<td>When I go to bed to when I get up in the morning did I go to the toilet?</td>
<td>Explanations for the SCCAI need to improve.</td>
</tr>
<tr>
<td></td>
<td>Patient 3 - No</td>
<td>I was a little unsure what this meant. Sometimes I would wake up at say 5am and need to rush to the loo but wasn’t sure if this counted.</td>
<td>Example: “Was your sleep disturbed by needing to get up to pass a bowel motion?”</td>
</tr>
<tr>
<td></td>
<td>Patient 4 - Yes</td>
<td>Well am I having to get up, am I woken by the fact that I need to go.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Patient 5 – Yes</td>
<td>From when I go to sleep to when I wake up.</td>
<td></td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index
2.3.11 Faecal calprotectin

The electronic communication between TrueColours UC and the IBDoc® Portal was successful. FCal results were imported into TrueColours UC and represented graphically (Figure 2-3, page 44).

2.3.12 Pathology results

Blood, endoscopy and histopathology results as well as a log of research samples could be entered manually into TrueColours UC (by the TrueColours research team) through an “External data” tab (Table 2-8 and Figure 2-4).

Table 2-8: List of results included in TrueColours UC

<table>
<thead>
<tr>
<th>Results</th>
<th>Abbreviation</th>
<th>Possible range limit (units)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bloods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haemoglobin</td>
<td>Hb</td>
<td>10-250 (g/L)</td>
</tr>
<tr>
<td>Platelets</td>
<td>Plt</td>
<td>10-1000 (x10^-9/L)</td>
</tr>
<tr>
<td>White Cell count</td>
<td>WCC</td>
<td>0-30 (x10^-9/L)</td>
</tr>
<tr>
<td>Albumin</td>
<td>Alb</td>
<td>10-50 (g/L)</td>
</tr>
<tr>
<td>Ferritin</td>
<td></td>
<td>0-800 (ug/L)</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td></td>
<td>0-85 (%)</td>
</tr>
<tr>
<td>C-Reactive Protein</td>
<td>CRP</td>
<td>0-400 (umol/L)</td>
</tr>
<tr>
<td><strong>Endoscopy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ulcerative Colitis Endoscopic</td>
<td>UCEIS</td>
<td>0-8</td>
</tr>
<tr>
<td>Index of Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nancy Index</td>
<td>Nancy</td>
<td>0-4</td>
</tr>
<tr>
<td><strong>Research bloods</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Plasma stored</td>
<td></td>
<td>1 = frozen sample of plasma stored</td>
</tr>
</tbody>
</table>
2.3.13 Medications

Medications could be entered, along with dose, frequency and duration. This was performed at the time of registration however could be altered by the patient or the TrueColours UC research team whenever a change was made. This information was displayed as a timeline above the SCCAI symptom graph to allow temporal correlation with symptoms and QoL (Figure 2-3). Hovering the cursor over each of the medication bars revealed the exact details entered.

2.3.14 Treatment Guidance

Each patient had four templates, corresponding to remission, mild, moderate and severe disease activity domains. Treatment guidance only appeared on the patient dashboard if the templates had been completed and approved by AW. The patient themselves could not amend the treatment guidance section however AW could modify it at any stage.
2.3.15 Pre-Pilot Results

Nine patients, 56% male, median age 34 years (IQR 15.1, range 30-46) completed 3 weeks of TrueColours UC questionnaires. The median System Usability Scale (SUS) score was 85 (IQR 10, range 75-92.5) which correlates with good usability (the SUS is explained in Chapter 4, section 4.2.1.2, page 79). No technical problems were encountered by the pre-pilot patients or the TrueColours UC research team. Patient feedback indicated that reminder email prompts needed to be more clearly marked and be at a greater interval (initially 1 hour) from the initial email prompt. These iterations were performed: the reminder interval was increased to 10 hours and was highlighted in red print.
2.5 Discussion

Adapting TrueColours Bipolar to TrueColours UC was successful. The result provided a system capable of recording symptoms, QoL, PROMs, FCal and external results (blood, endoscopy and histopathology results). It was also able to provide a medication timeline as well as personalised treatment guidance.

Other web-based systems have been successfully adapted to cater for multiple chronic diseases in paediatric practice. KLIK (a Dutch acronym for QoL in clinical practice), originally began collecting PRO data for children with juvenile arthritis (158, 159). It has now been implemented in over 30 disease groups in over 10 hospitals. As each new disease has been added, relevant PROM questionnaires have been added to the KLIK platform (160).

The most important consideration in this adaptation process was which questionnaires to incorporate. The aim was to obtain the most comprehensive overview of disease activity with minimal burden to the patient. Domains of disease activity assessment were researched and appropriate indices chosen.

The SCCAI symptom index required the most thought because of uncertainty as to whether patients could complete this reliably, independently and on a daily basis (152). Our data showed good to very good correlation with kappa values of 0.76 - 0.91 (Table 2-5) between patient and physician responses, providing evidence that patient responses were valid. Along with the advantages of accessibility and established thresholds for disease activity, this made the SCCAI the best choice for symptom monitoring. Thresholds and their colour coding became integral to daily monitoring. The traffic light system has been used in other medical
web based programmes (160) (161) but had not been previously used with TrueColours Bipolar.

All questionnaires were integrated into TrueColours UC platform without complication. There were minimal changes from their paper version. ISPOR recommendations were followed for three questionnaires (SCCAI, IBD-Control-8 and CUCQ-8) and cognitive debriefing revealed that the ePROMs replicated the paper versions. This is reassuring and is supported by previous meta-analyses (148, 149).

Incorporating FCal results within TrueColours UC was a first. IBDoc® usually operates through its own portal which physicians can access. Communication between TrueColours UC and the IBDoc® Portal API allowed these results to be plotted in TrueColours UC, below the SCCAI and QoL graphs. This successful integration demonstrates the flexibility of the TrueColours platform and its ability to adapt to the needs of different chronic diseases. It also indicates the potential for other technology platforms to be integrated in the future.

Treatment guidance was not part of the TrueColours Bipolar platform. This function required four templates (corresponding to different levels of disease activity) to be integrated and subsequent individualisation for each patient at registration. Guidance was restricted to topical rectal and oral 5-ASA medications alone. Readily available guidance regarding optimisation of these agents has been shown to improve outcomes with no adverse effects (65). Further studies will be required to examine the safety and efficacy of this approach.
The pre-pilot, although only for three weeks, was worthwhile. Importantly, no technical issues were encountered. Feedback did result in changes which were made prior to commencement of the 6 month pilot.

This adaptation has shown that the TrueColours platform is capable of modifications that enable disease-specific monitoring. If the methods detailed in this chapter are used as a guide, we believe that TrueColours could be adapted to any chronic disease process, allowing widespread collection of disease activity data and PROMs.

The remainder of this thesis is an analysis of using TrueColours UC for a 6 month pilot. The purpose of the pilot was to determine whether the adaptation had produced a feasible and usable tool that could allow assessment of disease fluctuation, treatment approaches, QoL and outcome measures in a way that might have a positive impact on patient care and facilitate research.
3 Chapter Three

Feasibility of TrueColours Ulcerative Colitis

3.1 Introduction

Feasibility is the state or degree of something being easily or conveniently done. A pilot is a small-scale test of methods and procedures which inform feasibility, pointing to necessary modifications (162). Despite their differences, the literature often confuses feasibility and usability. In this thesis, feasibility of TrueColours UC means to examine the approaches (methods and procedures) that are ultimately intended to be used in a larger study. Usability is the extent to which the TrueColours UC software can be used by patients to achieve specific goals and this is addressed separately in Chapter 4.

An example of a health technology pilot is a real-time smartphone solution for the management of women with gestational diabetes in Oxford, UK. In this study, glucometer readings were automatically transferred from a glucose meter (via Bluetooth) to a smartphone (via a preloaded software application) and from the smartphone to an NHS server. Feasibility was proven with a recruitment rate of 48% (50/104) and a retention rate of 96% (48/50). Adherence was good, with 85% of women recording the minimum number of blood glucose readings every week (163). Based on these results, little modification was required and a randomised trial has now begun to examine clinical, economic and satisfaction outcomes.

Another example is a pilot that was performed in the United States in 2012 which explored using text message reminders to encourage immunisation for infants. A recruitment rate of 72% (90/125) of parents approached was achieved, showing that parents were willing to provide mobile phone numbers to receive these reminders. The retention rate was 77%
This pilot revealed unanticipated loss of mobile phone service and the need for backup systems. These findings influenced the software chosen as well as the quantity of contact information collected from participants in the subsequent randomised trial (164).

The aims of this chapter are to evaluate the feasibility of the TrueColours UC methods and procedures, from initial patient identification to data analysis. Adherence to questionnaires, FCal, blood tests and sigmoidoscopies are also evaluated. These results will inform a future randomised controlled trial and or clinical implementation of TrueColours UC.
3.2 Methods

3.2.1 Number of Patients

Like all pilots, this was not a hypothesis testing study. The pilot sample size was based instead on the pragmatics of recruitment and the necessities for examining feasibility. We aimed to recruit approximately 60 patients.

3.2.2 Feasibility assessment

To consider feasibility, the study protocol must be considered (See Appendix A), represented as a flow diagram (Figure 3-1).

**Figure 3-1: Flow diagram of the TrueColours UC pilot**

![Flow diagram of the TrueColours UC pilot](image-url)
Multiple aspects of feasibility were examined:

- Patient identification
- Invitation to participate
- Inclusion and exclusion criteria
- Obtaining informed consent
- Recruitment rates
- Registration process
- Education and logistics
- Sample collection
- Retention rates
- Adherence to questionnaires
- Uptake and adherence to FCaL
- Adherence to blood tests
- Adherence to sigmoidoscopy
- Data capture and downloads

### 3.2.2.1 Patient identification

Between April 2016 and July 2016, the IBD outpatient clinic appointment lists were printed two weeks in advance. To determine which patients had UC and were aged between 18-65 years old, each clinic list was cross referenced with IBD Live, the IBD database used at the John Radcliffe Hospital. A diagnosis of UC on IBD Live was defined according to ECCO guidelines (165).

The IBD Cohort Study is a longitudinal cohort of IBD patients with well annotated phenotypes and genotypes linked to tissue samples. All IBD patients at the John Radcliffe
Hospital are invited to become part of this cohort (Research and Development Reference: 5864, Research Ethics Committee Reference: 09/H1204/30, HTA 12217). From IBD Live, it was possible to determine whether a patient had given written informed consent for the IBD Cohort Study, including permission to be contacted about research studies. IBD clinic lists and patient files were then examined on the day of the clinic to determine what proportion of patients (between the ages of 18-65 with UC) had been sent a letter. For those patients not sent an invitation, an invitation pack was offered and patients were asked to contact AW by email or phone if they wished to participate in the TrueColours UC pilot. Inpatient lists were also examined regularly to identify patients admitted for exacerbation of UC.

Demographics of all patients with UC on IBD Live were examined, including total number registered, gender distribution, median current age (years), median duration of disease (years), and worst ever extent of disease (Montreal classification (151)). Current biologic use for UC at the John Radcliffe Hospital was determined through the IBD biologics database. Biologics are a form of treatment for IBD which are prescribed for patients with moderate to severely active IBD when other treatments, such as mesalazine, steroids and immunosuppressants have not worked. There are several different biologics used in IBD including adalimumab, golimumab, infliximab and vedolizumab. In this thesis, these are referred to collectively as biologics.
3.2.2.2 Invitation to participate

From the above lists, eligible patients were mailed a Patient Invitation Letter (see Appendix G) which explained the TrueColours UC pilot and invited participation. Attached to this letter was a copy of the Patient Information Sheet (see Appendix H), Consent Form (see Appendix I) and TrueColours UC User Guide (see Appendix J). Inpatients with UC also received the same information, but this was hand delivered by one of the research team.

Patients were informed that the TrueColours UC pilot was a 6 month study and that their participation required the following:

- Being registered on TrueColours UC
- Daily emails from TrueColours UC, which provided the questionnaire link
- Home stool kit testing for FCaI
- Monthly blood tests
- A sigmoidoscopy within 1 month of registration and again at 6 months

At the IBD outpatient clinic, physicians were asked to enquire of those patients previously sent an invitation as to whether they were interested in participating. If interested, the research team would see the patient following their clinical consultation, or at another convenient time.
3.2.2.3 **Inclusion and exclusion criteria**

Inclusion and exclusion criteria were checked by the research team.

3.2.2.3.1 **Inclusion Criteria**

- Males or females aged 18-65 years
- Diagnosis of UC of any extent or severity
- The patient must have an email address
- Possession of a smartphone and regular internet access (a smartphone is a mobile phone with an advanced operating system which combines features of a personal computer and can access the internet and has a touchscreen user interface)
- Capacity to answer daily questions independently

3.2.2.3.2 **Exclusion Criteria**

- A diagnosis of CD or indeterminate colitis
- Planned extended (greater than 1 month) overseas travel within the following 6 months, if internet access would be impossible, inconvenient or unaffordable during this time
- Previous colectomy for UC
- Inability to communicate well with investigators or unable to comply with the study requirements

3.2.2.4 **Informed consent**

Patients were required to give written informed consent for the study approved by the local Regional Ethical Committee (LREC Reference 16/SC/0103) (see Appendix J).
3.2.2.5 Recruitment rates

Recruitment rates were calculated by number of patients recruited to the TrueColours UC pilot divided by number of invitation letters delivered (whether sent by mail or given in person).

3.2.2.6 Registration process

Once consented, patients were registered with TrueColours UC. The registration process required the research team to have a computer (iPad, laptop or desktop) and internet access. As detailed in Chapter 2, section 2.2.3, page 24, registration included:

- Entry of patient name, date of birth, email address and contact details
- Selection of questionnaires and associated frequency of email prompts
  - Clinical symptom index: SCCAI - daily
  - Disease-specific QoL: IBD Control-8 - fortnightly
  - Disease-specific QoL: CUCQ-8 - fortnightly
  - Generic QoL: EQ-5D - fortnightly
  - Personalised questionnaires (optional) – daily or weekly
  - Baseline demographic questionnaire within 1 month of registration
  - Follow-up ICHOM questionnaire at 3 months
- Establishing a link to IBDoc® to enable FCAl monitoring
- Entry of current medication
- Formulating personalised treatment guidance and discussing this with the patient

3.2.2.7 Education and logistics

Once registered, patients received a one-on-one education session on TrueColours UC. The TrueColours Online Tour which consisted of 20 slides about TrueColours UC was used as a
guide for this education. Patients were made aware that they had ongoing access to this information via the “Help” section of their TrueColours UC personal account. Education regarding IBDoc® FCal was performed using the IBDoc® video (166). This was followed by a manual demonstration of how to use the IBDoc® test kit (excluding an actual stool sample) and CalApp® (see Chapter 2, section 2.2.14, page 32).

TrueColours UC Patient Packs were assembled by the Clinical Trials Facility Nurses (funded by Local Clinical Research Network (LCRN) and Biomedical Research Centre (BRC)). Each pack was personalised at the time of patient registration.

This pack included:

- A schedule for proposed blood tests and sigmoidoscopies
- Labelled pathology forms for monthly clinical and research blood tests. Attached to each monthly blood request was a research form and two tubes (ethylenediaminetetraacetic acid (EDTA) and peripheral blood mononuclear cell (PBMC)), labelled only with the TrueColours UC number
- A labelled sigmoidoscopy booking request form
- Space for 6 IBDoc® stool kits (these needed to be refrigerated until the time of patient registration)
- A paper copy of the TrueColours User Guide (Appendix J)

Time taken to register and educate each patient was recorded in 5 minute intervals. Several days after each registration, AW checked TrueColours UC to ensure that questionnaires were being successfully submitted. If questionnaires had not been commenced, AW contacted the patient (via phone or email) to resolve the problem.
3.2.2.8 Sample collection

Clinical blood, endoscopy and biopsy samples were processed through the hospital laboratory. For research blood samples to be viable, these needed to be taken at the hospital between 9am to 4pm, Monday to Friday. Pathology forms were marked with the research team contact details. Once a blood sample was taken, the phlebotomist was asked to contact the Oxford Research Nurses for Immunology and Inflammatory Diseases (ORNIID), who would then collect and date the sample. This sample was then processed by a research assistant at the Weatherall Institute of Molecular Medicine (WIMM). Once processed, the date of each research sample was electronically recorded in each patient’s TrueColours UC file. Bloods taken outside the hospital were unable to be processed as research samples.

For research biopsies collected at sigmoidoscopy, this required that a member of the ORNIID team be present at the procedure for immediate processing of the sample (liquid nitrogen storage followed by transport to the WIMM). For this to occur, advanced notice of all sigmoidoscopy appointment times was required. A list of scheduled TrueColours UC sigmoidoscopy appointments was emailed (from AW to the ORNIID team) at least 3 days in advance.

3.2.2.9 Retention rates

For this pilot, retention rate refers to the continued completion of questionnaires. Patients could withdraw from the study at any time. If a patient chose to withdraw, or if colectomy was required for medically refractory disease, the questionnaire schedule was terminated by the TrueColours UC research team and no further email prompts were sent. If a patient withdrew from the pilot, another patient could be recruited.
3.2.2.10 Adherence to questionnaires

Adherence was defined as the number of questionnaires submitted, divided by the number of email prompts sent. One email prompt was defined as the initial email prompt as well as the reminder prompt if needed. This was calculated for the daily, fortnightly and personalised questionnaires. Importantly, patients were unable to skip questions they did not want to answer and questionnaires were only able to be submitted after all assigned questionnaires for that day had been completed. For example, if there were four questionnaires to be completed (one SCCAI symptom questionnaire and three QoL questionnaires), each questionnaire would automatically follow on with submission only possible when the last questionnaire was complete.

3.2.2.11 Uptake and adherence to IBDoc® faecal calprotectin (FCal)

Uptake of FCal testing was defined as the number of patients who performed at least one test. The denominator used was 66, because all patients received FCal kits. For those patients who did at least one test, adherence was defined as how many of the monthly tests (out of a total of six) were performed.

3.2.2.12 Adherence to blood tests

The number of patients completing monthly blood tests was documented.

3.2.2.13 Adherence to baseline and exit sigmoidoscopy

The number of patients completing baseline and exit sigmoidoscopies was documented.
3.2.2.14 Data capture and downloads

Questionnaire data were automatically transferred to the TrueColours UC site on the NHS server. External data such as blood, sigmoidoscopy and histopathology results required manual entry by the TrueColours UC research team (see Chapter 2, section 2.3.12, page 46). Data could be downloaded from TrueColours UC (in Microsoft Excel format) on a per patient or per questionnaire basis. Data were coded numerically (e.g., male = 0, female = 1) and therefore coding sheets were required to interpret the summary data. To use collection of ICHOM metrics (see Chapter 2, section 2.3.6.5, page 40) as an example, baseline and 3 month follow up data were downloaded and tabulated.
3.3 Results

3.3.1 Number of patients
A total of 66 patients were recruited from April 2016 to August 2016.

3.3.2 Feasibility assessment

3.3.2.1 Patient identification
Printing clinic lists in advance and cross referencing these with the IBD Live database captured 48% (184/380) of patients with UC between the ages of 18-65 years attending IBD clinics. IBD Live currently has 883 UC patients with available demographic data: median (IQR) age 46 years (25,60), male 50%, distribution of disease (E1 16%, E2 42%, E3 39%, unknown extent 3%), and median (IQR) duration of disease 10 years (5,14). At the time of TrueColours UC recruitment there were 156 UC patients currently receiving biologic therapy at the John Radcliffe Hospital. Assuming a current estimated total UC population of 1200 patients (not all patients captured on IBD Live), this gives a biologic use rate of approximately 13%.

3.3.2.2 Invitation to participate
184 invitation packs were mailed between April 2016 and July 2016. 16 information packs were returned stating incorrect address. 56 additional packs were given in person (50 in the IBD outpatient clinic and 6 to inpatients). The total number of invitation packs distributed was 240. A total of 76 patients expressed interest and were assessed for eligibility.
3.3.2.3 Inclusion and exclusion criteria

Of the 76 patients screened, 10 patients were excluded because they did not meet eligibility criteria: CD (n=1), previous colectomy (n=1), age over 65 years (n=1), no smartphone (n=6), no regular internet access (n=1).

3.3.2.4 Recruitment rates

A recruitment rate of 28% (66/240) was achieved. No information was gathered on those that were given an invitation but did not proceed.

3.3.2.5 Registration process

No technical or internet access difficulties were experienced with the registration process.

3.3.2.6 Education and logistics

Median (IQR) time taken for consent, registration and education was 30 minutes (25,35).

Four patients needed to be contacted within five days of registration as questionnaires had not been submitted: incorrect email addresses entered at the time of registration (n=3) or temporary lack of internet access (n=1).

3.3.2.7 Sample collection

For research samples, 91% (264/290) of research blood samples taken were successfully collected and processed. Reasons for non-collection of research samples were out-of-hours collection (after 4pm or weekend samples) (n=16), lack of communication between phlebotomist and laboratory staff (n=7) and laboratory staff annual leave (n=3). 98% (109/111) of biopsy samples were successfully collected and stored for research purposes.
(one sigmoidoscopy was re-scheduled without our knowledge and one sigmoidoscopy was performed after 6 pm when no laboratory staff were available).

### 3.3.2.8 Retention rates

Over the 6 month period, 9 patients withdrew from the TrueColours UC pilot. Each patient who withdrew was subsequently randomly assigned a patient number between 1 and 9 and a master list of this allocation was documented. Table 3-1 describes patients by this patient number, gender (M/F), age range (years), day of withdrawal and reason for withdrawal.

<table>
<thead>
<tr>
<th>Patient*</th>
<th>Day of withdrawal</th>
<th>Reason for withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1, F 40-49</td>
<td>15</td>
<td>Inconvenient to visit the hospital for additional blood and sigmoidoscopy requirements</td>
</tr>
<tr>
<td>Patient 2, M 30-39</td>
<td>0</td>
<td>Unhappy regarding volume of extra blood require</td>
</tr>
<tr>
<td>Patient 3, M 30-39</td>
<td>1</td>
<td>Employer not willing to allow time off work for research sample purposes</td>
</tr>
<tr>
<td>Patient 4, F 30-39</td>
<td>56</td>
<td>Colectomy for medically refractory disease</td>
</tr>
<tr>
<td>Patient 5, F 40-49</td>
<td>49</td>
<td>Not willing to have two sigmoidoscopies in a 6 month period</td>
</tr>
<tr>
<td>Patient 6, F 30-39</td>
<td>91</td>
<td>Considered TrueColours UC as a negative psychological reminder of ongoing disease activity</td>
</tr>
<tr>
<td>Patient 7, F 30-39</td>
<td>0</td>
<td>No reason given</td>
</tr>
<tr>
<td>Patient 8, F 50-51</td>
<td>0</td>
<td>No reason given</td>
</tr>
<tr>
<td>Patient 9, M 30-39</td>
<td>3</td>
<td>No reason given</td>
</tr>
</tbody>
</table>

*Patient numbers are randomly assigned and have no association with TrueColours UC number.
Table 3-2 reports the baseline characteristics of those patients who withdrew and those patients who completed the 6 month pilot.

**Table 3-2: Demographics of patients who withdrew vs completed the TrueColours UC pilot**

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Withdrew (n=9)</th>
<th>Completed (n=57)</th>
<th>Entire Cohort (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)</td>
<td>33%</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>Age (years) Median (IQR)</td>
<td>33 (33-40)</td>
<td>41 (32.0,50.0)</td>
<td>40 (32.0,48.8)</td>
</tr>
<tr>
<td>Duration of UC (years) Median (IQR)</td>
<td>2.5 (1.8, 3.5)</td>
<td>5 (0,11)</td>
<td>5 (1,11)</td>
</tr>
<tr>
<td>Worst ever extent of UC % (Montreal classification*)</td>
<td>E1 22% E2 33% E3 44% Unknown 0%</td>
<td>E1 21% E2 42% E3 33% Unknown 4%</td>
<td>E1 21% E2 41% E3 35% Unknown 3%</td>
</tr>
<tr>
<td>Tertiary education (%)</td>
<td>56%</td>
<td>60%</td>
<td>59%</td>
</tr>
<tr>
<td>Biologic use %</td>
<td>9%</td>
<td>47%</td>
<td>42%</td>
</tr>
<tr>
<td>Disease activity (SCCAI) at entry</td>
<td>Remission 25% Moderate 56% Moderate 11% Severe 11%</td>
<td>Remission 40% Moderate 19% Severe 0%</td>
<td>Remission 38% Moderate 42% Moderate 18% Severe 2%</td>
</tr>
</tbody>
</table>

IQR= Interquartile Range, *Montreal classification: E1=proctitis, E2=left-sided colitis, E3=extensive colitis
Biologic use includes prescription of infliximab, adalimumab or vedolizumab

3.3.2.9 Adherence to questionnaires

Table 3-3 shows adherence to questionnaires over the 6 month pilot including comparison of the first and last 3 month periods.

**Table 3-3: Adherence to questionnaires in the TrueColours UC pilot**

<table>
<thead>
<tr>
<th>Questionnaire</th>
<th>Number of patients</th>
<th>Total average adherence over 6 months</th>
<th>First 3 months</th>
<th>Last 3 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily SCCAI</td>
<td>63</td>
<td>76%</td>
<td>81%</td>
<td>72%</td>
</tr>
<tr>
<td>Fortnightly QOL</td>
<td>63</td>
<td>95%</td>
<td>96%</td>
<td>94%</td>
</tr>
<tr>
<td>Personalised (daily)</td>
<td>9</td>
<td>78%</td>
<td>84%</td>
<td>72%</td>
</tr>
<tr>
<td>Personalised (weekly)</td>
<td>4</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Once only demographic or outcome</td>
<td>63</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index
3.3.2.10 Uptake and Adherence to IBDoc® faecal calprotectin (FCal)

At least one FCal was used in 75% (48/66). Of those 48 patients, the median (IQR) number of monthly tests performed was 4 (3,5). Ten of the 48 patients had an invalid result recorded for one of their FCal results. This meant that the test cassette was read by their smartphone (via CalApp®, please see Appendix A), but failed to be processed correctly. Nine out of 10 of these patients went on to have valid results on subsequent tests.

3.3.2.11 Adherence to blood tests

The median (IQR) number of clinical blood tests performed on each patient was 5 (3,5). The median (IQR) number of research bloods taken and processed was 4 (3,5).

3.3.2.12 Adherence to baseline and exit sigmoidoscopy

The median (IQR) number of sigmoidoscopies performed on each patient was 2 (2,2).

3.3.2.13 Data Capture

Questionnaire data transfer and data downloads functioned well. Data were able to be accessed at any stage throughout the pilot. Table 3-4 displays the ICHOM data that were downloaded from the baseline and 3 month questionnaires.
Table 3-4: Baseline and three month ICHOM questionnaire data

<table>
<thead>
<tr>
<th>Question</th>
<th>Baseline ICHOM questionnaire relating to previous 12 months (n = 66)</th>
<th>ICHOM questionnaire relating to previous 3 months (n = 58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence to answering ICHOM questions</td>
<td>95%</td>
<td>100%</td>
</tr>
<tr>
<td>Level of education</td>
<td>None 5%</td>
<td>N/A (not re-asked at 3 months)</td>
</tr>
<tr>
<td></td>
<td>Primary 5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Secondary 31%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tertiary 59%</td>
<td></td>
</tr>
<tr>
<td>Smiling status</td>
<td>Never 58%</td>
<td>Never 58%</td>
</tr>
<tr>
<td></td>
<td>Ex-smoker 36%</td>
<td>Ex-smoker 36%</td>
</tr>
<tr>
<td></td>
<td>Current 6%</td>
<td>Current 6%</td>
</tr>
<tr>
<td>Extraintestinal manifestations</td>
<td>Eyes 9%</td>
<td>Eyes 5%</td>
</tr>
<tr>
<td></td>
<td>Skin 3%</td>
<td>Skin 0%</td>
</tr>
<tr>
<td></td>
<td>Joints 37%</td>
<td>Joints 28%</td>
</tr>
<tr>
<td></td>
<td>Liver 3%</td>
<td>Liver 2 %</td>
</tr>
<tr>
<td></td>
<td>Other 2%</td>
<td>Other 0%</td>
</tr>
<tr>
<td>Previous diagnosis of Hepatitis B, Tuberculosis or HIV</td>
<td>Hepatitis B 0%</td>
<td>N/A (not re-asked at 3 months)</td>
</tr>
<tr>
<td></td>
<td>TB 1.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>HIV 0%</td>
<td></td>
</tr>
<tr>
<td>Oral prednisolone use</td>
<td>None 58%</td>
<td>None 84%</td>
</tr>
<tr>
<td></td>
<td>&lt;3 months 24%</td>
<td>&lt;3 months 16%</td>
</tr>
<tr>
<td></td>
<td>&gt;3 months 18%</td>
<td>&gt;3 months N/A</td>
</tr>
<tr>
<td>Complications</td>
<td>13%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>pancreatitis (1)</td>
<td>pancreatitis (1)</td>
</tr>
<tr>
<td></td>
<td>medication reaction/intolerance (7)</td>
<td>medication reaction/intolerance (5)</td>
</tr>
<tr>
<td>Number of hospital admissions</td>
<td>0 = 77%</td>
<td>0 = 92%</td>
</tr>
<tr>
<td></td>
<td>1 = 17%</td>
<td>1 = 4%</td>
</tr>
<tr>
<td></td>
<td>2 = 1.5%</td>
<td>2 = 4%</td>
</tr>
<tr>
<td></td>
<td>3 = 1.5%</td>
<td>3 = 0%</td>
</tr>
<tr>
<td></td>
<td>4 = 0 %</td>
<td>4 = 0%</td>
</tr>
<tr>
<td></td>
<td>≥5 = 3%</td>
<td>≥5 = 0%</td>
</tr>
<tr>
<td>Median length of stay in days, range</td>
<td>5 days (range 1-21)</td>
<td>4 days (range 1-14)</td>
</tr>
<tr>
<td>Number of emergency department presentations</td>
<td>0 = 80%</td>
<td>0 = 93%</td>
</tr>
<tr>
<td></td>
<td>1 = 15.5%</td>
<td>1 = 1.7%</td>
</tr>
<tr>
<td></td>
<td>2 = 3%</td>
<td>2 = 3.5%</td>
</tr>
<tr>
<td></td>
<td>3 = 1.5%</td>
<td>3 = 1.7%</td>
</tr>
<tr>
<td></td>
<td>4 = 0%</td>
<td>4 = 0%</td>
</tr>
<tr>
<td></td>
<td>≥5 = 0%</td>
<td>≥5 = 0%</td>
</tr>
<tr>
<td>Diagnosis of bowel cancer</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

HIV = Human Immunodeficiency Virus
The manual entry of blood, sigmoidoscopy and biopsy results by the TrueColours UC research team was time consuming and errors occurred, including duplicate (n=33), incorrectly assigned (n=9), and missing (n=13) results. To ensure that no incorrect results had been entered, each patient’s laboratory and endoscopy entries were checked throughout the pilot period and again prior to analysis. Incorrect results were difficult to delete. Another negative aspect of manual entry of results was that there was often a delay in patients being able to access their results as the manual transfer of results was only performed on a weekly to fortnightly basis.
3.4 Discussion

This feasibility study of TrueColours UC supports the importance of pilot studies. This was a small-scale prospective non-randomised study recruiting UC patients to use TrueColours UC. This was the first time that TrueColours had been formally piloted in a condition other than bipolar disorder and so it was necessary to examine multiple aspects of feasibility prior to further implementation.

Adherence to questionnaires over the 6 month pilot was high for both daily (76%) and fortnightly questionnaires (94%). This corresponds well with adherence to responses in bipolar disorder where response to weekly texts over a 36 week period was 75% (68). Although there was a decrease in daily adherence between the first and last 3 months (81% and 72% respectively), this loss of 9% did not impact on obtaining an accurate account of disease trajectory. However, in contrast to a 6 month pilot monitoring gestational diabetes which has a finite endpoint (163), UC is a life-long condition, and so technology fatigue is likely to occur. Longer studies would need to assess this.

Retention for this pilot was almost 90%. It is important to note that TrueColours UC patients were self-selected, highly educated patients who consented to a 6-month study. It is therefore unlikely that one can extrapolate these results to either the long-term or the entire UC population. Of those patients who did withdraw from the pilot, it tended to be within the first few days with over half of patients stating that the reason for withdrawal was the requirement for additional blood and biopsy samples. Even if the blood and tissue samples were not required, it is unclear whether retention would remain this high over an indefinite period. Data collected in a clinical study versus implementation in clinic practice may also influence retention rates. Only nine patients withdrew from the pilot. As compared to those patients
completed the pilot, they were more likely to be female, younger, have a lesser duration of disease and a lower rate of biologic use. The only patient on biologic medication who withdrew did so because she required a colectomy for medically refractory disease.

Given that data download functioned well and all questionnaire information was stored without incident, data leak or loss on the NHS server, no changes are required to this component of TrueColours UC.

Although adherence and retention rates, data download and security all appeared reassuring, this pilot did highlight several problems with the feasibility of TrueColours UC which would need to be considered prior to commencing a larger study or wider clinical implementation. Some of these are practical realities and are thus subjective however need to be considered.

Improvement in patient identification strategies would be needed. Using the IBD Live database to prospectively identify patients from IBD outpatient clinic lists and then contacting these patients by post was somewhat inefficient. Firstly, only a proportion of UC patients were registered on IBD Live. Secondly, outpatient appointment lists often changed due to cancellations and urgent additions. This meant that despite attempting to invite all eligible patients, half of UC patients attending the IBD outpatient clinic had not received an invitation.

The ideal place to recruit a patient for TrueColours UC is at an IBD outpatient appointment however for clinical trials, at least 24 hours between receipt of information and consent is required.
For clinical implementation alone, patient identification would be much simpler as this could be done at the point of care. Creating increased awareness of the availability of TrueColours UC through posters, flyers, testimonials and social media would be more important in this context.

The recruitment rate for the TrueColours UC pilot was less than 30%. If patients had been given the option of electronic questionnaire participation only (that is, no need for FCal or additional blood tests or sigmoidoscopies above those required for normal clinical practice), the recruitment rate may have been higher. Multiple options for the level of participation (questionnaires only vs questionnaires plus FCal vs questionnaires plus FCal plus research samples) would be possible in a larger study. Further involving the entire IBD team regarding the benefits of TrueColours UC for both themselves and their IBD patients would also be a useful strategy (167).

In examining the demographics of those recruited, the median age of patients was 41 years which was comparable to the median age of 46 years of our IBD Live cohort. This pilot excluded patients above 65 years however, given that smartphone application studies in the elderly population (over 60 years) have been successful (168, 169), this was unnecessary and there will be no upper age limit in any future use.

Gender or distribution of disease did not appear to influence patient interest in TrueColours UC. Disease activity at entry into the TrueColours UC pilot was low (remission or mild) in greater than 70% of patients. Given the high percentage of patients on biologic medication (almost 50%), it can be assumed that greater disease activity had been experienced in the past
and this biased their motivation to be involved. A high percentage of tertiary education (58%) means that these results may not be applicable to all UC populations.

The infrastructure required for consent, registration and education for this TrueColours UC protocol was significant at a median of 30 minutes per patient. For further implementation of TrueColours UC, appropriate infrastructure would need to be in place to support these processes. To register a patient for questionnaires takes less than 5 minutes. This however, may need to be performed by a dedicated person within the IBD clinic (clinician or nurse) as the clinician seeing the patient at the outpatient clinic appointment may not have time to complete this process.

Adding research samples to this pilot did impact feasibility. It is likely that the requirement of additional samples did lead to a decrease in both recruitment and retention. Research blood samples were able to be taken from Monday to Friday, 9am to 4pm, at the John Radcliffe Hospital. These restrictions may have decreased the number of samples taken. Research samples also added to research and laboratory staff burden. For ongoing collection of research blood samples, it will be vital to collaboration with research and laboratory staff.

The logistics surrounding the coordination of available endoscopy appointments, appropriate endoscopists, patient availability and laboratory staff availability were difficult. Although 98% of all possible biopsies were collected, this took considerable effort and communication to arrange. Specially allocated research lists would allow better coordination of clinical, research and laboratory staff, however obtaining these lists is difficult in a unit with high clinical demand.
Manual entry of blood, endoscopy and histopathology results would not be feasible for a larger number of patients or for longer projects. For ongoing integration of this data, electronic patient results would need to be exported directly to TrueColours UC. For blood results, this is already occurring in Oxford with a programme known as Patient Knows Best (170).

In summary, the TrueColours UC platform with associated registration, questionnaire submission, data storage and retrieval is feasible and needs no further alteration. For those patients who were recruited, retention and adherence were good. It is the logistics surrounding patient identification, recruitment, transfer of laboratory results and the ongoing integration of research samples that provide ongoing challenges.
4 Chapter Four

Usability Assessment of TrueColours Ulcerative Colitis – a mixed methods study

4.1 Introduction

Real time monitoring in UC requires patients to enter symptom, QoL and outcome data. TrueColours UC is a web-based programme that was designed to have the capability to collect these data in a manner that displays data to the patient, as well as to medical and research teams (see Chapter 2). A high level of usability is essential for TrueColours UC to succeed. The Medical Research Council sensibly recommends that patients assess the usability of interventions before scaling-up programmes (171).

The aim of this chapter is to assess the usability of TrueColours UC. Usability is best assessed through a mixed methods approach (172). Mixed methods research requires the investigator to gather both quantitative and qualitative data, and to interpret the results based on the combined strengths of both datasets. Quantitative and qualitative research methods arise from different paradigms, but the core assumption is that the collective strength provides a better understanding of the question than either alone (173, 174).

Quantitative approaches to usability assessment deploy standardised questionnaires (175). A standardised questionnaire is designed for repeated use, specifying the set of questions, order, format and rules for calculating the total score. Standardised results offer advantages including objectivity, replicability, quantification, economy and communication of results (176).
The System Usability Scale (SUS) (177) was chosen for quantitative usability assessment in TrueColours UC. The SUS is the most widely used standardised usability questionnaire. There are several attributes that made it a good choice (178).

- It is technology agnostic, meaning that it can be used to assess a wide range of technologies. This was important for the TrueColours UC pilot, because patients used a range of devices (smart phones, laptops, desktops)
- It is quick and easy to use
- It provides a single score on a scale that is easily communicated (see below)
- It is non-proprietary, making it a cost-effective tool

The purpose of the qualitative component of this work was to provide a detailed perspective of patients’ interaction with TrueColours UC with a specific emphasis on factors that influence usability. Qualitative studies in health care generally involve interviews or focus groups (179). Qualitative assessment of usability was based on the Enhanced Usability Model which assesses usability by exploring efficiency, effectiveness, satisfaction, learnability and data security (180).

Other web-based monitoring programmes in IBD have not tested usability. This is in contrast to a mobile health monitoring programme in heart failure (SUPPORT HF, Seamless User-centred Proactive Provision Of Risk-stratified Treatment for Heart Failure), another chronic disease (181). Mixed methods were used to assess the usability of this programme. Quantitative analysis used a patient questionnaire, adherence rates, time taken to complete tasks and rate of successful first attempts. 76% of 54 patients responded positively when asked (via a quantitative questionnaire) whether they would like to use this programme as
part of their routine care (182). Qualitative analysis, through face-to-face interviews, showed SUPPORT HF to be user-friendly, with most participants stating that they would like to use it in the future. Other concepts emerged from the qualitative interviews including that SUPPORT HF provided a sense of connection with the healthcare provider, that embedding monitoring into a daily routine was useful and that there was a need for personalisation of the device (183). These concepts were incorporated into the current mixed methods study of TrueColours UC.

This chapter explains the process, results and subsequent importance of mixed methods analysis for usability assessment in TrueColours UC.
4.2 Methods

A mixed methods study was undertaken. Quantitative and qualitative data were collected and analysed in parallel. Findings were compared to determine whether they supported or contradicted each other.

4.2.1 Quantitative methods for usability assessment

4.2.1.1 Patient Selection

At the end of the 6 month pilot, or soon after withdrawal from the pilot, a TrueColours UC email prompt containing a link to the SUS questionnaire was sent. Patients who had registered fewer than two responses were excluded from receiving this email. Those patients participating in a qualitative interview (n=28), completed the SUS at least two days before the interview, with the research team blinded to the results. No SUS was completed in the presence of the research team. Patients were aware that the SUS results would be linked to their TrueColours UC file and that answers were not anonymous.

4.2.1.2 System Usability Scale

The SUS contains 10 questions, each on a 5-point scale of strength of agreement with the final score ranging from 0-100 (Figure 4-1). Higher scores indicate better usability. Calculation of the SUS requires care. Each question (1-10) has a total score of 4. For questions 1,3,5,7,9 the number is scale minus 1. For questions 2,4,6,8,10 the number is 5 minus scale. The total of this score is then multiplied by 2.5 to get a result out of 100. A total summary score was calculated by integrating this formula into TrueColours UC.
Figure 4-1: System Usability Scale

1. I think that I would like to use this product frequently.
2. I found the product unnecessarily complex.
3. I thought the product was easy to use.
4. I think that I would need the support of a technical person to be able to use this product.
5. I found the various functions in the product were well integrated.
6. I thought there was too much inconsistency in this product.
7. I imagine that most people would learn to use this product very quickly.
8. I found the product very awkward to use.
9. I felt very confident using the product.
10. I needed to learn a lot of things before I could get going with this product.

*When the SUS is used, patients were asked to score the following 10 items with one of five responses that range from Strongly Disagree (answer=1) to Strongly Agree (answer=5)

In terms of evaluating whether a product is acceptable, the SUS is a useful guide of overall product usability. Products that are at least passable have SUS scores above 70, with better products gaining scores in the high 70’s to upper 80’s. Truly superior products get scores greater than 90. Products with scores <70 require increased scrutiny and continued improvement and should be judged marginal at best (184).

Although the single number generated by the SUS is useful, explaining what a specific score means (for example, 75) is difficult. A 7-point adjective rating scale was introduced to determine if it was of any assistance in better explaining the overall experience. Correlation between the adjective rating and SUS score was high at \( r = 0.81 \) (184). Due to this, the adjective scale was added to the SUS for assessment of TrueColours UC (Figure 4-2).
Figure 4-2: 7-point adjective scale of the System Usability Scale

Overall, I would rate the user-friendliness of this product as:

| Worst imaginable | Awful | Poor | OK | Good | Excellent | Best imaginable |

4.2.2 Qualitative methods for usability assessment

The aim of the qualitative study was twofold: first to assess the usability of TrueColours UC and second to explore what impact TrueColours UC might have on patients. This chapter reports the findings on usability. The findings on the impact of TrueColours UC are reported in Chapter 5.

4.2.2.1 Patient Selection

At the end of the 6 month pilot or soon after withdrawal from the pilot, purposive sampling was used to invite thirty patients (via email) to take part in a face-to-face interview to provide feedback on TrueColours UC. Age, gender, disease activity at entry to the study (as determined by the SCCAI on the day of registration), and adherence rates to daily questionnaires were used to ensure that the qualitative cohort was representative of the total cohort. Attached to the invitation email was an Interview Patient Information Sheet (see Appendix L), which explained that the purpose of the interview was to obtain feedback about TrueColours UC and that participation was voluntary.

4.2.2.2 Interview Guide

A semi-structured interview guide was designed (see Appendix K). This required several iterations (AW, MP). Two early interview transcripts were read by MP and one by ST. This did not result in any changes to the interview guide.
4.2.3 Interviews
Audio-recorded face-to-face interviews were conducted (AW, between September 2016 and January 2017) at the John Radcliffe Hospital, in a private room to establish a confidential atmosphere. AW was known to each patient, having been the primary contact for the study period. Before each interview consent was obtained for audio-recording, confidentiality was emphasised and patients were offered the Interview Patient Information Sheet to re-read. Patients were encouraged to be as honest and open as possible about their experience. Transcripts were not returned to the participant for comments.

4.2.4 Transcription and coding
All interviews were transcribed verbatim and anonymised by an external professional transcription service (Clearview Transcript (185)). AW re-listened to each interview before reading the transcript. The raw data (i.e. the transcripts) were coded using NVivo 11, a qualitative data analysis software package (186). To determine appropriate codes, MP and AW independently coded (pen and paper) two transcripts; ST and AW independently coded another. After coding of these first three interviews, AW and MP met again to discuss individual codes and to reach agreement about the set of codes. All initial transcripts were then re-coded once codes were agreed.

4.2.5 Analysis
The portion of the qualitative interviews relating to the usability of TrueColours UC is reported in this chapter. A deductive approach was used to analyse the data based on five components of the Enhanced Usability Model: effectiveness, efficiency, satisfaction, learnability and data security (180).
The themes were defined as follows:

1. Effectiveness: How well do patients achieve the goals of submitting questionnaires and logging into their personal TrueColours UC page

2. Efficiency: What resources are consumed to these achieve goals

3. Satisfaction: How do patients feel about their use of TrueColours UC

4. Learnability: Time taken to learn the steps required to use TrueColours UC – both for questionnaires and the personal TrueColours UC page

5. Data security: concerns regarding personal data being stored on TrueColours UC

Codes relating to each theme were grouped together. An iterative process was used to develop the final coding. When new codes emerged during the analysis, these were added to the existing structure. The final structure for the usability analysis is displayed below in Table 4-1.

**Table 4-1: Qualitative coding structure for the TrueColours UC usability analysis**

<table>
<thead>
<tr>
<th>Themes</th>
<th>Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>Device used&lt;br&gt; Email prompts&lt;br&gt; • Frequency of prompts&lt;br&gt; • Reminders prompts&lt;br&gt; • Link to questionnaires&lt;br&gt; • Link to personal page&lt;br&gt; Difficulties with internet access/data coverage</td>
</tr>
<tr>
<td>Efficiency</td>
<td>Ease of use&lt;br&gt; Time taken to complete questionnaires</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>Experience with TrueColours UC&lt;br&gt; • Positive&lt;br&gt; • Negative&lt;br&gt; Interface (what it looked like)</td>
</tr>
<tr>
<td>Learnability</td>
<td>Submission of Questionnaires&lt;br&gt; Personal page&lt;br&gt; • Graphs&lt;br&gt; • Blood results&lt;br&gt; • Dot plots&lt;br&gt; • Notes section&lt;br&gt; • Side panel</td>
</tr>
<tr>
<td>Data security</td>
<td>Security concerns</td>
</tr>
</tbody>
</table>
4.2.2.6 Data saturation

There are no standard tests to estimate the sample size necessary to achieve data saturation in qualitative studies, but data saturation tables can be used to ensure that sufficient data have been collected to provide a comprehensive and credible analysis (187). After internal discussion, between 20 and 30 patients was considered likely to achieve data saturation. A prospective data saturation table was completed as the interviews progressed.

4.2.2.7 Reporting

The Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist was used to ensure explicit and comprehensive reporting (188). This checklist was developed to encourage explicit and comprehensive reporting of qualitative studies. Seventy-six items from 22 checklists were compiled to form a 32-item checklist to help researchers to report important aspects of the research team, study methods, context of study, findings, analysis and interpretation.
4.3 Results

Patient demographics of the qualitative cohort, quantitative cohort and total cohort are presented in Table 4-2.

Table 4-2: Demographics of qualitative cohort, quantitative cohort and entire cohort

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Qualitative Cohort (n=28)</th>
<th>Quantitative Cohort (n=59)</th>
<th>Entire Cohort (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male)*</td>
<td>46%</td>
<td>44%</td>
<td>44%</td>
</tr>
<tr>
<td>Age (years)*, Median (IQR)</td>
<td>41.5 (32.2,47.2)</td>
<td>41.0 (32.0,49.5)</td>
<td>40.0 (32.0,48.8)</td>
</tr>
<tr>
<td>Duration of UC (years), Median (IQR)</td>
<td>5.5 (1.75,14.8)</td>
<td>5.0 (0.5,11.0)</td>
<td>5.0 (1.0,11.0)</td>
</tr>
<tr>
<td>Worst ever extent of UC (%) (Montreal classification) *</td>
<td>E1 14%</td>
<td>E1 20%</td>
<td>E1 21%</td>
</tr>
<tr>
<td></td>
<td>E2 46%</td>
<td>E2 42%</td>
<td>E2 41%</td>
</tr>
<tr>
<td></td>
<td>E3 36%</td>
<td>E3 34%</td>
<td>E3 35%</td>
</tr>
<tr>
<td></td>
<td>Unknown 4%</td>
<td>Unknown 4%</td>
<td>Unknown 3%</td>
</tr>
<tr>
<td>Tertiary education (%)</td>
<td>68%</td>
<td>61%</td>
<td>59%</td>
</tr>
<tr>
<td>Smoking status (%)</td>
<td>Never 68%</td>
<td>Never 58%</td>
<td>Never 58%</td>
</tr>
<tr>
<td></td>
<td>Ex-smoker 29%</td>
<td>Ex-smoker 37%</td>
<td>Ex-smoker 36%</td>
</tr>
<tr>
<td></td>
<td>Current 3%</td>
<td>Never 5%</td>
<td>Current 6%</td>
</tr>
<tr>
<td>Prednisolone in last 12 months (%)</td>
<td>&lt;3 months: 25%</td>
<td>&lt;3 months: 25%</td>
<td>&lt;3 months: 24%</td>
</tr>
<tr>
<td></td>
<td>&gt;3 months: 25%</td>
<td>&gt;3 months: 20%</td>
<td>&gt;3 months: 18%</td>
</tr>
<tr>
<td>Hospital admissions in last 12 months (%)</td>
<td>21% (median 0)</td>
<td>22% (median 0)</td>
<td>23% (median 0)</td>
</tr>
<tr>
<td>Emergency department presentations in last 12 months (%)</td>
<td>18% (median =0)</td>
<td>19% (median 0)</td>
<td>20% (median 0)</td>
</tr>
<tr>
<td>Biologic use (%)</td>
<td>57%</td>
<td>47%</td>
<td>42%</td>
</tr>
<tr>
<td>Disease activity (SCCAI) at entry to (%)*</td>
<td>remission 39%</td>
<td>Remission 39%</td>
<td>Remission 38%</td>
</tr>
<tr>
<td></td>
<td>mild 36%</td>
<td>mild 41%</td>
<td>mild 42%</td>
</tr>
<tr>
<td></td>
<td>moderate 21%</td>
<td>moderate 19%</td>
<td>moderate 18%</td>
</tr>
<tr>
<td></td>
<td>severe 4%</td>
<td>severe 2%</td>
<td>severe 2%</td>
</tr>
<tr>
<td>IBD-Control 8 at entry, Median (IQR)</td>
<td>8.0 (4.8,14.0)</td>
<td>9.0 (5.0,14.0)</td>
<td>9.0 (5.0,14.0)</td>
</tr>
<tr>
<td>Adherence to daily questionnaires (%)*</td>
<td>81%</td>
<td>80%</td>
<td>79%</td>
</tr>
<tr>
<td>Adherence to fortnightly questionnaires (%)</td>
<td>99%</td>
<td>98%</td>
<td>97%</td>
</tr>
<tr>
<td>Time spent on internet each day (hours) Median (IQR)</td>
<td>3.0 (0.4,0.0)</td>
<td>3.0 (1.0,5.25)</td>
<td>3.0 (1.0,4.5)</td>
</tr>
<tr>
<td>Use of social media (%)</td>
<td>78%</td>
<td>83%</td>
<td>83%</td>
</tr>
<tr>
<td>Withdrawn patients (day of withdrawal)</td>
<td>2/28 (49.91)</td>
<td>2/59 (49.91)</td>
<td>9/66 (0.0,0.1,3,15,49, 56,91)</td>
</tr>
</tbody>
</table>

* Items used for purposive sampling, IBD-Control 8: Best score =16, Worst score=0. Use of social media included Facebook, Twitter, Instagram or other, Montreal classification: E1: proctitis, E2:L-sided colitis, E3: extensive colitis (151), unknown = answer given by patient and maximum extent unclear in medical notes
4.3.1 Quantitative results for usability assessment

Of the 66 patients recruited to TrueColours UC, 61 patients fitted the criteria and were emailed the SUS questionnaire. There was a 97% (59/61) completion rate. The two non-responders were patients who withdrew at Day 15 and Day 56. The median (IQR) SUS result (n=59) was 92.5 (80,95) (Figure 4-3), and weighted average of the adjective rating scale was 5.7 (Figure 4-4).

**Figure 4-3: Graphical representation of the System Usability Scale results**

*Best possible SUS score is 100. Brackets: the half-open interval $(a, b]$ includes all values greater than $a$ and less than or equal to $b$.

**Figure 4-4: Graphical representation of the 7-point adjective scale results**

Rating x axis: 1 = worst imaginable, 2 = awful, 3 = poor, 4 = OK, 5 = good, 6 = excellent, 7 = best imaginable
4.3.2 Qualitative results for usability assessment

28/30 (93%) of invited patients were interviewed. The reason that two patients declined was lack of time to visit the hospital. Most patients were interviewed alone; four had a relative in the room (one child, two partners, one mother). For usability assessment, data saturation was achieved at interview number 19 (see Appendix M).

Despite a range of age, gender, disease activity at entry, and adherence rates to daily questionnaires (Table 4-2), patients reported that TrueColours UC was a usable system. Each component of the Enhanced Usability Model is documented below. The qualitative results pertaining to what impact TrueColours UC had on patients is explored in Chapter 5.

For the qualitative results in this thesis, “most” refers to greater than 75%, “many” refers to greater than 50% and “some” refers to approximately 30% of patients. Patient interviews were anonymised. Each patient interviewed was randomly assigned an interview number between 1 and 28 and a master list of this allocation was documented. Patients are described by their interview number, gender and age range. For example, Interview 5, M 30-39 means that Interview 5 was male and between 30-39 years old.

4.3.2.1 Effectiveness

There was unanimous agreement that TrueColours UC functioned as intended. No technology issues were reported, with patients receiving their email prompts as arranged and being able to log into their personal account at any time. Illustrative comments include:

“It [the email] prompts me into a link, and I just click on the link, and there’s another button saying to start the questionnaire, you follow the set of questions and then submit” [Interview 27, F 18-29]
Smartphones, tablets, laptops and desktops were used in a range of different destinations when travelling. No challenges were mentioned by the patients regarding any of the devices.

“Monday to Friday would be on my PC at work, keyboard and mouse and at weekends I would do it on my phone and occasionally on my iPad.” [Interview 1, M 30-39]

“Yes pretty much always on my phone and that was the good thing about being on holiday, it came through and was easy to do. You know, you’re going to be looking at your phone for Facebook so why not….it goes in….you answer your email, in it goes.” [Interview 4, M 40-49]

Most patients liked the reminder function (a follow up email received if there had been no answer to the daily email within 10 hours) (Chapter 2, section 2.3.3, page 35).

“I found it [the reminder email] really useful because the amount of times I’d forgot, it would just flash up. Normally at home where I was able to sit down for five minutes and able to do it.” [Interview 22, F 30-39]

Lack of data or Wi-Fi access was the primary reason for patients not answering questionnaires. Other reasons included forgetting to complete or not accessing emails on the days in question. Importantly, these reasons were not due to lack of effectiveness of the TrueColours UC system.

“I live in an area where internet connection is very poor and there were some days when I couldn’t actually logon to emails to do it. Well for me [not answering], Wi-Fi about 90% to be honest.” [Interview 6, F 50-59]

Two patients, [Interview 9, M 20-29] and [Interview 17, F 30-39], suggested having this system as an app rather than a web-based programme to overcome this difficulty with internet access.
4.3.2.2 Efficiency

Most patients thought that TrueColours UC was efficient. The daily questionnaire took less than one minute and the fortnightly questionnaire less than five minutes.

“I check my daily emails, there it is. You click on it, you’re given a series of questions, it takes all of 30 seconds and you’re done” [Interview 8, M 40-49]

“For the fortnightly ones, it couldn’t have been more than five minutes.” [Interview 22, F30-39]

Some patients did comment that there was a lot of repetition in the fortnightly QoL questionnaires. The reason for this is that three QoL questionnaires were included for the TrueColours UC pilot: IBD Control-8, CUCQ 8 and EQ-5D (Chapter 2, section 2.3.6.2, page 38). These patients suggested that it would be helpful if only one measure was used however they did not express a view as to which one they liked best. An illustrative example of this is:

“There is a lot of overlap in the fortnightly questionnaires. Even though it didn’t take very long, it was a bit annoying.” [Interview 13, F 60-65]

4.3.2.3 Satisfaction

Overall, satisfaction was good with most patients expressing that their experience with TrueColours UC was positive.

“I think that it’s great and I had no issues with it. I found it really useful and just yes, well set up and it works well.” [Interview 7, M30-39]

“I am very satisfied with it.” [Interview 9, M 20-29]

Most patients liked the presentation of TrueColours UC both in how the questionnaires and personal account appeared on their device. However, some patients did mention that the graphs were sometimes difficult to see when a smartphone was used.
“The phone you can’t see the graph very well, even if you turn it sideways it doesn’t seem to spread out, it a bit squished up, but for everything else it is alright.” [Interview 23, F 30-39]

Many patients incorporated TrueColours UC into their daily routine. The below quotes are from patients with daily questionnaire adherence rates over 90%.

“It just feels now, part of the routine of my every day. I have to take tablets and at 7:58am I’ll get an email and I’ll fill that out and it just feels like part of the management and the routine.” [Interview 7, M 30-39]

“It just become part of my daily routine so it’s probably something that actually once it’s all over with, it’s something I’d probably miss.” [Interview 22, F 30-39]

“I’ve kind of got used to it now. It’s just a thing that you do every day. I get to work, I log into my computer, I start to load up stuff and then while I am waiting for that I just fill this is and, like I say, it so quick, it’s just part of the routine. [Interview 23, F 30-39]

For the patients who used the treatment guidance section, satisfaction appeared good. Some patients didn’t use the advice section at all however overall satisfaction with the system did not seem to be affected by this.

“Yes, I increased my pentasa on a couple of occasions when I had a little bit of a frowny face, and again that was good for me rather than having to ring up the doctor and say do you think I should do this? It was almost, the system was saying to me right okay we need to do something here.” [Interview 6, F 50-59]

As a marker of satisfaction, we asked whether patients would like to use TrueColours UC in the future and most of the patients involved in this pilot did express that they wanted to continue use it.

“I would be happy to do the online data for the foreseeable future, no problem.” [Interview 8, M 40-49]
“Yes, I would love to continue with this.” [Interview 10, M 30-39]

4.3.2.4 Learnability

The questionnaire component TrueColours UC was easy to learn. This included following the email prompt, filling out and submitting the questionnaires. Some patients did have problems with their TrueColours UC personal account. This is the home page which patients were directed to after questionnaires were completed. It displayed their daily score (with the corresponding colour and smiley face) and allowed patients to navigate to their graphs and results as desired.

The colour coding of the symptom (SCCAI) graph was well liked by all and was the focus for most patients’ opinion of their personal account. Some patients had difficulty with the interpretation of QoL graphs and dot plots (see Appendix J for examples). Titles and labelling were thought to be inadequate and the bi-directional nature of the SCCAI symptom graph and the IBD-Control graph was confusing for some patients. These factors prevented optimal use of these graphs. Some patients did not know where to find information such as blood results.

“I found the system very straightforward. Yes, just playing around with it yes. As I said it’s very self-explanatory isn’t it? I mean I’m quite interested in it anyway so I go through the tabs to see if there’s anything that’s been added as well.” [Interview 19 F 40-49]

“It was a good indicator rather than maybe just a number. A visual is a good indicator, a colour was a good indicator, the visual face was a good indicator, up, down, that’s good. I think if you just gave me a seven, I don’t know what I would take from that. With a bit of colour and with a horizontal face you think, actually yes I am a little bit more like that rather than a big green smiley face, rather than giving me a 10 or a 1.” [Interview 3, M 40-49]
“On the IBD-Control [graph], the labelling needs to be improved. It is not clear to me where best and worst is, especially if showing this at appointment, consultants who aren’t familiar with this, then it would be easier. As the symptoms decrease, this graph increases which is a bit confusing.” [Interview 9, M 20-29]

“I think maybe….sometimes I thought maybe if there’s a page [link] there. Sort of like, okay, what does this mean, questions and answers.” [Interview 25, F 40-49]

“To be honest it’s [the dot plots] are hard to understand and I didn’t really know what the big blobs meant.” [Interview 4, M40-49]

4.3.2.5 Data Security

No patients had concerns about data security that would stop them from using TrueColours UC. Many patients had not even considered data security in this setting.

“I think there is lots of security issues regarding data and IT to be concerned about. But I don’t think this is one of them.” [Interview 8, M 40-49]

“It’s not really something that I have ever thought about. If it was my money or bank account that would be different. My health, actually I think that the only way we move forward with health care is to actually research it and have information and have data and people willing to do it. [Interview 14, M 50-59]
4.4 Discussion

This mixed methods study evaluated the usability of TrueColours UC. Although good levels of usability were found in both the quantitative and qualitative analyses, it was the comparison of these two sets of results that allowed a comprehensive picture of the current usability of TrueColours UC and how it could be further improved.

The quantitative results showed that TrueColours UC is a usable product, with a median SUS of 92.5. The adjective rating scale reinforced this, with most patients rating TrueColours UC as good, excellent, or best imaginable. Although this was encouraging, it was unclear from the SUS score alone what problems there were with TrueColours UC and how it could be improved.

The qualitative interviews provided in-depth and useful information regarding TrueColours UC. Overall, the interviews reflected the findings from the SUS however were far more useful as each domain of usability was carefully explored. As in the SUPPORT HF study (183), it was the qualitative component that guided further improvements.

One impediment to effectiveness of TrueColours UC was lack of internet access and or mobile data coverage for some patients. The continuing growth and penetration of mobile data services will ultimately remove this barrier. Further development of TrueColours UC to include an ‘app’, which can function independently of internet access, may offer another option. HealthPROMISE (53) (see Chapter 1, section 1.2.2.3, page 15) is an example of an ‘app’ that is being trialled in IBD to enable collection of PROMs.
Even though TrueColours UC was efficient, we believe that this can be further improved by decreasing the three QOL measures currently asked, to one, the IBD Control-8. IBD Control has been endorsed by the ICHOM and is a validated patient-reported outcome measure (97).

Throughout the qualitative interviews, it became clear that there were different levels of engagement with the system. Most patients reported good satisfaction with TrueColours UC although some were not aware of or were not using all functionalities offered (e.g., blood results, treatment advice, personalized questions). How this relates to the patients’ interpretation of satisfaction is difficult as not all patients will want to use TrueColours UC in the same way. However, further education on what is available within the system could be provided to ensure that it is then patient choice rather than a lack of knowledge that informs their decision.

The colour coded SCCAI symptom graph was popular. The colours assisted with interpretation of the graph with patients relating to the traffic light concept well. Conversely, for the QoL graphs, confusion arose due to the labelling of the graphs and the axes being inadequate. Brundage et al (189) reported that patients liked line graphs for their individual data display however, like in this study some patients had difficulty with the bi-directional nature (as the symptom graph increases, the QoL graph decreases) of graphs. We feel that this confusion will be decreased when labelling of the graphs is improved. Other suggestions such as providing the opportunity to access further information through placing a small question mark on the graph, that if selected, would provide the user with more information needs to be considered.
By focusing on keeping what the patients liked about TrueColours UC, and considering the above improvements, there is potential to improve TrueColours UC.

In terms of study limitations, this was a cohort of 66 patients with five patients withdrawing from the trial at an early stage (within 1 day). For these five patients, it was not possible to assess the usability of the system given their lack of engagement. The demographics of these patients were similar to the remainder of the cohort. For the 61 patients who did commence TrueColours UC, it could be argued that they were a highly motivated and educated cohort (over 60% had tertiary education) who had consented to a 6 month pilot. It is unclear whether the above usability can be transferred to the UC population as a whole.

In conclusion, this mixed methods analysis has revealed that TrueColours UC is a usable web-based programme for patients with UC. If we had used the SUS results alone, an opportunity to improve the system would have been missed. Further iterations with repeat and continued evaluation to achieve the best possible usability are required. Once this has been achieved, TrueColours UC could successfully be used in a randomised trial to evaluate cost effectiveness or in clinical practice to collect patient-reported outcomes data.
Chapter Five

A qualitative study exploring patient perception of TrueColours Ulcerative Colitis

5.1 Introduction

It has been recognised that new technologies in healthcare, such as web-based systems for monitoring chronic disease, have the potential to change the dynamics of how patients monitor and manage their own health (190). A shift from a paternalistic to a collaborative approach means that patients need to be actively involved in their own care (191). This involvement results in patients understanding their health needs better (192) while at the same time having the potential for clinical and economic benefit (193, 194).

Web-based management has been shown to be beneficial in chronic conditions including diabetes (195), hypertension (196) and asthma (20, 197). Management tools have increased patient confidence, communication (197) and improved disease control (20, 196).

Early attempts at personalised self-management of UC were encouraging. In 2001, Robinson et al (18) randomised 203 patients with UC undergoing hospital follow-up to patient-centred self-management training and follow-up on request (intervention group), or normal treatment and follow-up (control group). For the intervention group, relapses were treated more quickly (difference 35 hours [95% CI 16.4-60.2], p<0.0001), with fewer visits to hospital (difference 2.0 visits per year [95% CI 1.6-2.7], p<0.0001) or primary care physician (difference 0.6 [95% CI 0.2-1.1]). Although this was not a web-based programme it showed that patient-centred self-management in UC can be successful.
Monitoring of UC through Home Automated Telemanagement (HAT) has also showed promise during 6 months of weekly monitoring (198, 199). Qualitative interviews at exit from the study showed that HAT was well accepted, resulted in increased awareness about the disease and facilitated greater control of their symptoms (199).

Constant-care (50, 65), a web-based programme for mild to moderate UC reported that 88% of the 169 patients randomised to the web-based programme preferred this approach to conventional care. No qualitative interviews assessed patient perception of the programme, but the authors reported patient-empowerment in the web-based group, judged by increased self-initiation of treatment, shorter relapse times, increased adherence to medication and increased knowledge regarding IBD. The programme resulted in increased disease-specific quality of life and a decrease in requests for outpatient appointments.

Chapter 4 addressed the usability of TrueColours UC using a mixed methods approach. The focus of this chapter is to analyse, report and discuss patient perspectives regarding TrueColours UC, exploring how TrueColours UC impacted on patient management.
5.2 Methods

This chapter reports the findings on the impact that TrueColours UC had on patients.

5.2.1 Patient Selection

Patient selection and recruitment methods are described in Chapter 3.

5.2.2 Interview guide

The interview guide (see Appendix K) was designed to ask opened-ended questions for patients to describe their experience with TrueColours UC and the impact that it had on them and their management of UC, in addition to questions related to usability.

5.2.3 Interviews

Interviews were conducted as previously described in Chapter 4 (Chapter 4, section 4.2.2.3, page 82).

5.2.4 Transcription

All interviews were anonymized and transcribed verbatim by an external professional transcription service (Clearview Transcript (185)). Transcripts were coded in NVivo11, a qualitative data analysis software package (186). AW re-listened to each interview before reading the transcript.
5.2.5 *Coding and analysis*

To determine appropriate codes, MP and AW independently coded (pen and paper) two transcripts; ST and AW independently coded (pen and paper) another (n=3). After coding these three interviews, AW met with ST and MP separately to discuss individual codes and reach agreement about the final set of codes. Transcripts were then coded, including re-coding of the initial three.

The difference between this component of the qualitative work compared to the usability assessment (Chapter 4, section 4.2.2.4, page 82), was that the process of coding and analysis was inductive. The outcome was therefore themes that emerged from the interview transcripts during the analysis. Codes relating to each theme were grouped together. An iterative process developed the final coding structure. New themes that emerged as the interviews progressed were added to the existing structure.

5.2.6 *Data saturation*

A data saturation table was created to ensure that no new themes were emerging in later interviews and that no new insights were likely to be gained by conducting further interviews. A prospective data saturation table was completed as interviews and analysis progressed.

5.2.7 *Reporting*

The Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist was used to ensure explicit and comprehensive reporting (188) (see Chapter 4, 4.2.2.7, page 84).
5.3 Results

A total of 28 face-to-face interviews were conducted. Demographics indicate that patients interviewed were representative of the entire cohort (Table 4-2). For impact of TrueColours UC, data saturation was reached at interview number 20 (Appendix M).

In this chapter, ‘most’ refers to greater than 75%, ‘many’ refers to greater than 50% and “some” refers to approximately 30% of patients. Patient interviews were anonymised. Each patient interviewed was randomly assigned an interview number between 1 and 28 and a master list of this allocation was documented. Patients are described by their interview number, gender (M/F), age range (years). For example, [Interview 5, M 30-39] means that Interview 5 was male and between 30-39 years old.

Sub-themes that emerged from the analysis were:

- Awareness
- Control
- Decision making
- Reassurance
- Communication
- Burden of Treatment

After evaluating the sub-themes, the central theme that emerged was patient empowerment. The central theme of empowerment was implicit in the sub-themes rather than an explicit terminology used by patients. It should be noted that not all sub-themes were significant for each patient.
5.3.1 Awareness

Awareness was defined as whether a patient recognised their UC as a health issue and whether TrueColours UC monitoring informed them of the level of activity of their disease (eg whether in remission or active disease). Most patients believed that receiving and answering the questionnaires alone increased their awareness about their UC. Many patients mentioned that email prompts helped them to prioritise their health. Some patients became more aware of triggers for their symptoms such as lack of sleep or missing medications.

“I think it made me more aware of it, instead of just brushing it to the side.”
[Interview 22, F 18-29]

The daily SCCAI symptom score, colour-coded smiley face (see Figure 2-2, page 43) and the symptom graph (see Figure 2-3, page 44) made patients aware of the severity of their symptoms. Some patients found that being able to access results for their FCal testing (Figure 2-3, page 44) and/or blood tests helped them gain an overall picture of their disease activity.

“The best thing [about TrueColours] was the monitoring, being able to monitor. I know that I keep repeating myself but I think that it is just monitoring my progress, and it’s nice to see in having the results recorded, not just the results that I’m answering questions to but the blood results, the stool samples, that sort of thing. I’m quite interested in that and looking at my progress. And it’s been really good because I’ve been doing it every day, and we’ve been looking at it and seeing how it’s tracking it, looking at the numbers. Because I’ve been talking to other people about it and they say what number are you today and all that kind of stuff.” [Interview 19, F 40-49]

Some patients revealed that monitoring made them aware that their UC was not as well controlled as they had previously thought.

“It made me stop and think because I thought that I was alright and I clearly wasn’t.”
[Interview 23, F 30-39]
5.3.2 Control

Control was defined as patients feeling that they had the power to influence the course of their management. Many patients felt that their personalised record gave them “greater control over their disease”. This sense of control came from a variety of sources. Some patients reported that having access to an accurate record of their disease activity made them more able to evaluate what was happening with their disease. This made them more confident about what their next steps needed to be. This may have been whether they needed to seek help or to act as reassurance that everything was going well.

“It’s given me the confidence to know when I need to visit here, or when I need to talk to somebody and when not.” [Interview 6, F 50-59]

“It feels like I’ve got more control, because I’ve got something to physically look at and tell me, it’s not in my head, it’s telling me it’s bad and I need to do something.” [Interview 10, M 30-39]

Many patients commented that knowing that health professionals were also able to see or had access to their information made them feel safer and more cared for. This subsequently led to a sense of control over the situation.

“You’re in control because you’re giving constant feedback, constant reviews whereas if you didn’t have this and you just relied on your NHS quarterly, six monthly, whatever it is appointment, you sometimes feel a bit, I’m in the NHS, I’m in the system, I’m forgotten, but it does actually feel like you’re communicating with somebody so it does give you….feel like you’re in control and you’re being looked after.” [Interview 3, M 40-49]

For some patients, a feeling of control was also achieved through motivation to be more responsible for their health and to take ownership of the problem.
“I think that it increases my sense of control. I think that it gives – the onus back on to me, to take some responsibility.” [Interview 28, F 60-65]

Many patients used the personalised treatment guidance section because it allowed them to make changes in their treatment and encouraged contact with the IBD team if this advice was not effective or if they required more information.

“Well I like the idea of having more on time monitoring and being able to respond to problems timely through the advice given rather than waiting very long periods for appointments.” [Interview 9, M 18-29]

5.3.3 Decision making

A variety of important clinical decisions need to be made when managing UC. Making decisions about their management, particularly in regard to changes in medication was reported as one of the most difficult aspects of managing UC for some patients. These patients found the symptom graph useful as they felt that they were basing their decisions on an accurate record. As an example, while using TrueColours UC, some patients found that they were more able to identify if their current medication was not satisfactory and that a change in medication may be useful.

“I think that it is more about reflection. Being able to see, no I don’t think I’ve been doing well so therefore I think I need something to change.” [Interview 11, F 18-29]

“I think it’s making sure that people have the ability to have a look at their symptoms and see what’s working and what isn’t working so that a sensible decision can be made.” [Interview 28, F 60-65]

Conversely, some patients commented that it was helpful to use TrueColours UC monitoring after a change in medication had been made as it ensured that they were being monitored for symptom improvement.
“At the point when I signed up my symptoms had been really problematic and I’d been finding it quite difficult to actually see if it was getting any better. I’d been on different treatments for a while and I didn’t feel like it was improving at all. So it was quite good to have something that enticed me to record my symptoms every day, then being able to look back at it and think, okay it’s not perfect but it is getting better.” [Interview 27, F 18-29]

5.3.4 Reassurance

Reassurance was defined as the patient feeling that they felt less afraid, upset, or doubtful about their UC. Many patients commented on the negative impact that UC has had on their lives and the psychological burden that this often carried. Some patients reported dwelling on their symptoms and feeling anxious or depressed about having UC. Through answering the daily questionnaires and entering this data into their dashboard, they reported that the process allowed them to progress with other parts of their day. Reassurance that this information was recorded seemed to anecdotally help patients psychologically.

“I like to de-compartmentalise problems so once I’d written something down, I can close the book on it and that’s it. I think that I felt like that with TrueColours. So once I’d put in that I’d had a horrific night, what would have happened before TrueColours is that I’d spend the whole day thinking, “God I’ve had a horrific night” whereas if I had put it down, the data, I’d parked it, it had gone and I didn’t think about it again because I was actually then thinking, well let’s see what tomorrow brings. Psychologically I was able to look forward rather than back.” [Interview 5, F 30-39]

“I’m upset by it [my UC]. It becomes a bit more clinical to me which makes me feel better about it, because it is something that I can just submit an answer to. Once the questionnaire is done I don’t have to think about it whereas I think that I used to dwell on it.” [Interview 27, F 18-29]

Some patients mentioned that by answering the range of questionnaires they realised that other patients must experience many of the things that they have experienced, such as anxiety or fatigue. This realisation was reassuring for these patients as it helped them to understand the disease better and feel more able to speak about these aspects of their symptoms.
“It was so reassuring to see that other patients must also feel anxious and tired at times, otherwise those questions would not be there, would they? That has helped me to feel better about these things as I haven’t wanted to say anything about this in my appointments.” [Interview 10, M 30-39]

5.3.5 Communication

Exchanging information is integral to patient-centred care. It was unanimous that TrueColours UC monitoring had a positive impact on communication. Having both symptom and quality of life graphs available proved to be a powerful tool for patients. The impact on communication was reported on many levels: communication with IBD nurses, communication with IBD specialists, feeling connected to the hospital and improved communication with family members.

5.3.5.1 Communication with IBD specialist nurses

IBD specialist nurses are often the first point of contact for UC patients experiencing an exacerbation of symptoms. Initial contact is primarily though the IBD-advice telephone line. Patients reported that often they were uncertain about when to call and many were concerned about wasting nurses’ time or being unable to describe accurately how unwell they felt. Patients reported that TrueColours UC monitoring helped appropriate timing and content of communication.

“So, I felt very safe. As soon as I got TrueColours I felt safe whereas before I had that, you know I would constantly be thinking “God am I causing problems? Am I being a bit of a drama queen?” I didn’t want to interrupt people and the IBD nurses especially unless it was something serious. But this [TrueColours UC] identified actually this is the time to raise your hand and say you need help.” [Interview 5, F 30-39]
“If I went up into the amber after being in the green, I would give the advice line a call, say I am concerned, it’s gone up, it’s saying I’m getting worse.” [Interview 15, M 50-59]

5.3.5.2 Communication with the IBD specialist

Most patients welcomed the prospect of TrueColours UC monitoring being available at a consultation. Specialist access to TrueColours UC was not part of the pilot, but some patients used their smartphones to show their graphs to their treating specialist. Those patients who did felt that it was a positive experience. The main reason for patients believing that it would enrich their consultations was that it provided their specialist with a more accurate picture of their symptoms over the period since they were last seen.

“I would like my dashboard to be seen at the consultations as it would give a true record of my symptoms and would help my specialist to see what was happening to me and what the best treatment might be.” [Interview 19, F 40-49]

“I think I was unable to provide him with a true picture of how I was because I could go through a month of being unwell but at the point I saw him, be well. So actually he was getting a really false picture of how I was all the time. Had I been able to go to him with this, I think he would have identified that there was a part that probably wasn’t working as it should be and before the inflammation took over and caused such devastation, we may have been able to try something different sooner.” [Interview 5, F 30-39]

There were many patients who felt that they did not intentionally give a false picture at a medical consultation, but that their recall of symptoms was often inadequate.

“Because I’ve definitely been one of those people who finds that you get to the appointment and you’re like I’ve been pretty good, but actually you haven’t been feeling that great, so not really giving an accurate picture.” [Interview 11, F 18-29]

Many patients felt that TrueColours UC would improve communication about aspects of their health such as anxiety. Patients reported that they were reluctant to mention their anxiety or
difficulties with coping and that physicians tended not to ask about these aspects. If this information was on the screen for the doctor to see, it was felt that it might facilitate the conversation.

“I liked that TrueColours recorded answers about feeling anxious. At the beginning a lot of my consultant appointment were about the treatment plan. And I bottled up how I was actually feeling with it. And I was really, really down at times and I didn’t feel like that was an important thing to talk about with my consultant. I didn’t feel that I could talk to them about the fact that I was really depressed.” [Interview 27, F 18-29]

5.3.5.3 Communication with family members

An unexpected finding was that some patients reported a significant improvement in health-related communication with partners or relatives. Patients used TrueColours UC to facilitate communication in different ways. Examples ranged from patients filling out questionnaires with their partner, to using the graphs to explain the symptoms, to discussions about anxiety and how family members might be able to help. Patients who shared TrueColours UC reported greater understanding or compassion within the home environment.

“Well over a six months period, that’s a lot of days, 150 odd days, bits come out. Over a length of time they get a good understanding, or more of an understanding than if I did nothing and I only went for my quarterly appointment. I’m going to the hospital today, okay good luck, that’s that but over 6 months of answering the same questions or just making a random comment, I’ve got to do my weekly review. All of this information goes into your partner’s mind and gives them…which then feeds back with them…it’s good to know that they understand. It’s good to know that they’re…because they understand they support a bit more. It’s thought provoking, its word provoking. It makes you talk.” [Interview 3, M 40-49]

“So a lot of the time, no matter how close to people you are, my husband and my mum are my two closest people and they can’t understand. They just can’t, as hard as they try. But I actually, with me being able to provide this data, provide them and educating them and showing them this is what I am going through. And it made me feel more like I was getting the support that I needed rather than the support that they felt I needed.” [Interview 5, F 30-39]
5.3.5.4 Feeling connected to the hospital

TrueColours UC monitoring happens outside the hospital setting. Email prompts and questionnaires were answered within the patient’s home or work environment, with patients themselves entering over 95% of the data collected. Patients did have the opportunity to contact the research team if there were concerns about their health (as an additional avenue of contact above standard care). By entering their own data and having this additional point of contact if needed, many patients perceived a closer connection to the hospital. Some patients felt that they were receiving support and that they were more valued.

“I think the care that I have had has always been very good here but there’s a psychological aspect because it feels like you’re connecting with the hospital everyday. It feels like you are more supported, like there’s more of a framework. “ [Interview 27, F18-29]

“This whole system has made me just sort of be – feel like I’m getting more care from the hospital even though really I’m doing the work.” [Interview 7, M 30-39]

“Before doing TrueColours, I definitely felt not that I was ignored but I was just sort of a bit of nothing, a person they just had to see in clinic, and we will send them for this. It really feels like there is someone at the end of the computer, and it seems a bit more like someone cares a bit more. It seems like people are paying a bit more attention.” [Interview 10, M 30-39]

5.3.6 Burden of Treatment

Chronic diseases such as UC result in multiple medical appointments over many years which place a burden on the patient, independent from the burden of symptoms. Patients reported that appointments often involve time off work, travel and long waiting times. There were many patients who reported that they would be happy to use TrueColours UC monitoring to avoid scheduled clinic appointments if they were well. Patients felt that this would be to their advantage by minimising disruption to their daily lives.
“I’d be happy to have this monitored remotely and not come in if I was well. Obviously there’s time off work, travelling to come here, so if there was – if I decided to come to the JR just to have a brief meeting to say that everything’s fine and then go back to work again, it’s sort of – an hour or two out of work, travelling half an hour up the A40 and half an hour back down so yes if that could happen, that would be beneficial for everyone I think because obviously then you always have more time to deal with other things as well so I think everyone would have more time.” [Interview 1, M 20-29]

Some patients were happy with the concept of remote monitoring provided that they could be seen when they needed to be seen. Patients were normally concerned that if they did need to be seen there would be long waiting times to return to the clinic.

“Yes, I didn’t need to come last month or whenever it was. I would have liked not to have come in so long as I felt that number one, my symptoms were being looked after and looked at. And number two, I know that I can ring up and make an appointment and I don’t have to wait three months to get back into the system as it were.” [Interview 3, M 30-39]

Two patients highlighted that using TrueColours UC as a remote monitor may be better for those with long standing disease rather than new diagnoses. Patients with a new diagnosis would prefer to maintain face-to-face contact until they felt more confident with their disease management.

“I’m still in the infancy of…I’ve not had this thing for six months really so it would be nice to continue to have that contact.” [Interview 4, M40 -49]

“I wouldn’t miss the face-to-face contact, no. Maybe because I have had it for such a long time and I’m fairly confident now when I need to come up and when I don’t.” [Interview 6, F 50-59]

As well as decreasing their own burden, there was acknowledgment of the current pressures on the NHS and how this may be alleviated by using remote monitoring effectively.
“I’m very conscious of how much pressure, especially financial pressure, is on the NHS at the moment. And I think that anything that can help with that and alleviate that, from both perspectives, you know, the doctors her and the patient’s time travelling and parking, is a good thing. And I don’t think that this is me being fobbed off and not being able to see a doctor.” [Interview 15, M 50-59]
5.4 Discussion

This qualitative study shows that patients perceive self-monitoring to have many benefits. Patients reported that TrueColours UC had a positive impact on awareness, control, decision making, reassurance and communication. Patients also thought that TrueColours UC had the potential to decrease their treatment burden. This can be interpreted as empowering the patient to take a greater role in their own management.

Empowering patients means providing them with the opportunities and support to develop the skills, confidence and knowledge to move from being a passive recipient of care to an active partner in their health care. Integrating medical technologies into daily life can enhance empowerment, because it is the patient who needs to deal with their condition between doctors’ appointments (192, 194). Such self-management has been found to support patient knowledge, behavioural change and self-efficacy, with a positive effect on patients’ overall well-being (192).

Wagner et al (200) emphasise that productive patient-clinician interactions are essential to optimise chronic disease management. Patients in our study perceived that there was improved communication on many levels: patient-IBD nurse, patient-IBD specialist and patient-relative. There are many studies that provide evidence that using PROMs improve patient-clinician communication (183) (201-206). One study (201) suggested that completion of PROMs allowed oncology patients to express their concerns more effectively, which prompted discussion with the physician. This was also the perception of some TrueColours UC patients, specifically regarding symptoms such as anxiety, that they had been previously reluctant to mention.
Santana et al (207) also observed the positive effect of PROMs on patient-relative communication in lung transplant patients. This potential benefit of TrueColours UC had not been considered prior to patients raising it in the interviews. Studies of mobile health monitoring in heart failure patients showed that electronic daily self-monitoring led to feelings of increased connectedness with the hospital, reassurance and increased confidence (183). Another heart failure mobile monitoring programme reported on patient perceptions after daily measurements and symptom entry for 6 months (208). Similar to TrueColours UC, these heart failure patients reported that they were more aware, less anxious, more accountable for their own health and more confident. It therefore appears that even though oncology, transplant, heart failure and UC are different chronic diseases, similar benefits arise from electronic self-monitoring.

It has been suggested that routine use of PROMs in chronic care management could aid shared decision making (209). This is likely to be the case, because patients in our study felt that an accurate record of their disease activity (as opposed to conventional recall) allowed them to determine whether a treatment change should be considered.

Electronic monitoring has the potential to decrease clinic visits. This has been reported in heart failure tele-monitoring (210). Patients in TrueColours UC welcomed the idea of real time monitoring making better use of appointments, although patients were seen as normal during the pilot. This is an emerging concept that recognises the increasing demands that are being placed on patients (211). Not only do patients have the burden of their symptoms, but also a burden of treatment. Further studies are necessary to determine the utility and cost effectiveness of TrueColours UC for the NHS or other Healthcare system, as well as exploring patient views on minimising disruption to their lives.
The TrueColours UC cohort was representative of the general Oxford UC cohort (Chapter 3, section 3.3.2.1, page 64). Nevertheless, it is likely that they were a highly motivated group of patients because they were self-selected. Rates of tertiary education were high and this may have contributed to the reported impact of TrueColours UC and should be considered when extending such a programme. This selection bias is a potential limitation of the study. It is therefore unclear whether these findings can be extrapolated to the UC population as a whole. Only two of nine patients who withdrew from the study were willing to be interviewed. Of the 9 patients who withdrew from the study, three did so after at least 4 weeks of monitoring. Only two of these three patients were willing to be interviewed.

In conclusion, patient perception of TrueColours UC monitoring was extremely positive. Self-monitoring empowers patients and may be a way of decreasing burden of treatment. TrueColours UC merits consideration for more widespread implementation to determine whether it helps manage capacity and demand in the chronic disease of ulcerative colitis and its value to the NHS.
6 Chapter Six

Development of a prediction score for escalation of therapy at an outpatient appointment in patients with known ulcerative colitis

6.1 Introduction

Ulcerative colitis (UC) places a treatment burden on patients as well as placing considerable demands on health service provision and costs. In the UK, most patients with UC rely on outpatient-based treatment initiated by a physician (generally every 3-12 months). Yet as with most chronic diseases, UC follows an unpredictable course, so fixed appointments rarely coincide with disease relapse, resulting in high non-attendance rates and delayed access for patients in need of urgent attention (212).

To address this, patient initiated clinics (PIC, also known as open access clinics) have been trialled in IBD. In contrast to conventional management, outpatient appointments are not regularly scheduled by the physician, but requested by the patient when needed. Kennedy et al randomised 19 hospitals caring for 700 patients with IBD in North West England to 10 control sites (n=403) and 9 intervention sites (n=297). At the intervention sites, consultants were trained in patient-centred care and introduced the intervention (written self-management plan and PIC) to eligible patients. Patients at the control sites had conventional care with fixed appointments. Over one year, self-managing patients made fewer outpatient appointments (difference -1.04; 95% CI -1.43 to -0.65; p<0.001) with lower non-attendances rates (difference -0.08; 95% CI -0.15 to -0.01; p=0.03) (213).
This cluster-randomised study followed a single-centre trial led by some of the same investigators (18), whereby 203 patients with UC were randomised to PIC (intervention group) or conventional management (control group). The time between symptom flares and treatment was significantly reduced in the PIC group compared to the control group (14.9 (SD 19.1) hours vs 49.6 (SD 65.1) hours; p<0.001). Patients in the PIC group made significantly fewer hospital and primary care outpatient appointments (0.9 vs 2.9 per patient per year, difference 2.0; 95% CI 1.6 to 2.7; and 0.3 vs 0.9 per patient per year, difference 0.6; 95% CI 0.2 to 1.1; p<0.006, respectively). Despite concerns about safety (such as failure of patients under PIC management to contact the service when unwell), a systematic review found no evidence of harm in any of eight PIC studies in different conditions, including IBD. Patients also reported better satisfaction in PICs compared to usual care (212).

Regular PROM assessment can be used to evaluate the need for an outpatient appointment. This offers an alternative to PIC management and has the potential to improve resource utilisation (214). Nevertheless, using PROMs as the basis for outpatient follow up of chronic disease is largely unexplored (215).

An exception is AmbuFlex (161), a generic system using both electronic and paper-based, disease-specific PROM data collection. As of December 2015, AmbuFlex has been implemented in Denmark in 15 outpatient clinics for nine diagnostic groups: epilepsy, narcolepsy, sleep apnoea, prostate cancer, asthma, renal failure, rheumatoid arthritis, colorectal cancer and coronary heart disease. One aim was to optimise healthcare utilisation, using PROMs and a traffic light system to identify those needing clinical attention, based on disease-specific algorithms. Over 70% of outpatient appointments for patients with epilepsy
at participating hospitals adopted AmbuFlex, generating 8256 patient-responses, for which half (48%) needed no appointment.

No such system has been trialed in IBD. Like AmbuFlex, the PROMs in TrueColours UC could be used, but it would help to have a prediction model that identified patients likely to require escalation of therapy if they attended an outpatient appointment. This would facilitate management and provide confidence to patients and physicians.

Multivariable risk prediction models are being developed in most medical domains to assist clinical decision-making. A multivariable prediction model uses a mathematical equation that relates multiple predictors from an individual to the probability or risk of the presence (diagnosis) or future occurrence (prognosis) of an outcome (216, 217).

Prediction modelling may develop a new model, validate an existing model, or investigate the impact that a model has on decision-making and patient outcomes (218). When developing a new model, probability estimates are commonly derived by combining information from multiple predictors, observed or measured from an individual (219), since a single predictor is unlikely to provide a reliable estimate of probability (220).

In IBD, some prediction models have been developed:

- management of acute severe ulcerative colitis (ASUC) (221, 222)
- prediction of risk of ASUC at initial diagnosis (223)
- risk of developing colorectal cancer in IBD (224)
- risk of relapse in CD (225)
- prediction of steroid failure in acute severe colitis (226)
Using one of the above models as an example, further explanation of the prediction of risk of ASUC within 3 years of diagnosis is explored (223). For this model, the development cohort included patients aged 16-89 years, diagnosed in Oxford and followed for 3 years. Multivariable logistic regression examined the adjusted association of 7 risk factors with ASUC. Backwards elimination produced a model that was then simplified to create an easy-to-use index. In Oxford, there were 34 episodes of ASUC in 111 patients within a median of 14 months (range 1-29) of diagnosis. The final model applied the sum of 1 point each for extensive disease, CRP > 10mg/L, or Hb < 12 g/dL for females and < 14 g/dL for males at diagnosis to give a score from 0/3 to 3/3, with 3/3 predicting a 70% risk of developing ASUC within 3 years. External validation performed in Cambridge, UK and Uppsala, Sweden included different proportions with ASUC (Cambridge 25/96 and Uppsala 18/298). Of those scoring 3/3 at diagnosis, 18/18 (Cambridge) and 12/13 (Uppsala) subsequently developed ASUC. Discriminative ability (c-statistic) was 0.81 Oxford, 0.95 Cambridge and 0.97 Uppsala.

The aim of the analysis in this chapter was to develop and internally validate a model that would predict the likelihood of escalation of therapy at an outpatient appointment for a patient with UC.
6.2 Methods

Data for prediction modelling were derived from the 6 month TrueColours UC pilot. The development of the prediction model has been guided by the TRIPOD statement (218).

6.2.1 Demographics

Patient selection and recruitment methods are described in Chapter 3.

6.2.2 Outcome measurement

The outcome to be predicted was escalation of therapy, defined as commencement of or any increase in therapy, including topical rectal mesalazine, topical rectal prednisolone, oral mesalazine dose, oral prednisolone, intravenous hydrocortisone, biologic medication, hospitalisation, or the need for dietetic or surgical consultation. Conversely, de-escalation of therapy was defined as cessation or any decrease in the above therapies. The decision to alter therapy was made by the physician (IBD Consultant, Fellow or Gastroenterology Registrar) seeing the patient at the IBD clinic, independently of data from TrueColours UC. Phone calls to the advice line, emails or consultation with IBD nurses were excluded from the analysis.

6.2.3 Independent review

Each patient’s paper hospital medical file was retrospectively examined by Dr Pavetha Seeva (PS), a physician who was independent to clinical decision-making for the 6 month TrueColours UC pilot. PS had no access to or experience with TrueColours UC. Each outpatient appointment was documented by date and need for escalation of therapy or de-escalation of therapy. Changes in therapy during inpatient admissions were excluded from the analysis.
6.2.4 Predictors

Dates of each patient’s outpatient appointments were cross-matched with the corresponding TrueColours UC electronic record, enabling all variables collected by TrueColours UC on those dates to be retrieved. These variables will be referred to as ‘predictors’ in this chapter. If the above predictors were not available, they were coded as ‘missing’.

- SCCAI (0-19) on day of (preferable) or within 5 days before the outpatient appointment
- IBD Control-8 (0-16) within 2 weeks before the outpatient appointment
- IBDoc® faecal calprotectin (FCal) within 4 weeks before the outpatient appointment
- Blood tests on the day of (preferable) or within 2 weeks before the outpatient appointment
  - haemoglobin (Hb) in g/dL
  - white cell count (WCC) in $10^9$/L
  - platelet count (Plt) in $10^9$/L
  - C-reactive protein (CRP) in mg/L
  - albumin (Alb) in g/L
  - transferrin saturation in %
  - ferritin in mcg/L

These data were then merged in an Excel table so that date of the outpatient appointment, outcome (escalation of therapy vs no escalation of therapy) and predictor data were tabulated.
6.2.5 Sample size

Effective sample size in prediction studies is based on the number of events, not the number of participants. Sample size estimates for developing multivariable models are based on the ratio of the number of outcome events (in this case, escalation of therapy) to the number of predictors examined, referred to as events per variable (EPV). A minimum EPV of between 5 and 10 is recommended to avoid overfitting. Overfitting means that when there are large numbers of predictors relative to the number of events, there is a greater chance of erroneously selecting weak or uninformative predictors and fitting idiosyncrasies to the data. Overfitting leads to worse prediction in independent data. Simple models involving few predictors are easier to apply in clinical practice. Analysis was consequently restricted to the ten potential predictors described above.

6.2.6 Missing data

Missing data were assumed to be missing completely at random and handled through multiple imputation. Multiple imputation means that values were assigned to missing data points. In practice this is achieved by random selection of value from a set of observed values closest to the predicted values from a specified (imputation) regression model. For this analysis, this was performed through the function ‘aregImpute’ in the R software (227). Imputation allows retention of the original sample size. If all patients with missing data were excluded, the sample is not only reduced, but may become biased and unrepresentative of the whole cohort.

6.2.7 Logistic regression model

Logistic regression was used to predict escalation of therapy. Logistic regression is a method for analysing a dataset in which there are one or more independent variables that determine a
binary outcome. The outcome measured was escalation (coded as 1) or no escalation (coded as 0). The goal of logistic regression is to find the model that best describes the relationship between the outcome of interest (in this case, escalation of therapy) and the independent predictors (in this case, SCCAI, IBD Control-8, FCaI, Hb, WCC, Plt, CRP, Alb, transferrin saturation and ferritin).

Selection of predictors for inclusion in the model was based on backwards elimination. Backwards elimination is an automated variable selection method that initially includes all potential predictors, which are then sequentially removed from the model until a pre-specified stopping rule is satisfied. The conventional stopping rule is the Akaike information criterion [AIC] equivalent to a p-value of 0.157.

Logistic regression then generates the coefficients of a formula to predict a logit transformation of the probability of the outcome in question.

\[
\text{logit} (p) = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \ldots + b_kX_k
\]

where \( \text{logit} (p) = \log \left( \frac{p}{1-p} \right) \), \( b_0 \) is the intercept, \( b_i \) are the coefficients of the logistic regression model, and \( X_i \) are the predictors.

Additional models were developed that took account of predictors likely to be useful in clinical practice

- SCCAI alone
- IBD Control-8 alone
- SCCAI plus IBD Control-8
SCCAI plus IBD Control-8 plus FCal

6.2.8 Model performance

The performance of each model was assessed in terms of calibration and discrimination.

6.2.8.1 Calibration

Calibration reflects the agreement between the predictions from the model and what was actually observed. In a well calibrated model, for patients with a predicted risk of x%, then x out of every 100 should experience the event. Predicted probabilities were calculated for all individuals in the data set. These probabilities were then ranked from smallest to largest and 10 equal size groups were created. In each of these 10 groups, the mean predicted probability of escalation of therapy was calculated and then the proportion who actually received escalation of therapy. These values were plotted against each other to create a calibration curve. In an ideal model, the calibration curve has a slope of 1 (45°), indicating perfect agreement between observed proportions of escalation of therapy and the predicted probability of escalation of therapy over the range of probabilities. The calibration intercept should be close to 0.

6.2.8.2 Discrimination

Discrimination describes how well the prediction model separates those with and without the event (that is, escalation of therapy). This is quantified by the concordance index (c-statistic, area under the receiver operating characteristic curve). A c-statistic of 0.5 indicates no discrimination (no better than random), whereas a c-statistic of 1.0 indicates perfect discrimination (that is, all patients requiring escalation of therapy have a higher predicted probability compared to patients who do not need escalation of therapy). The c-statistic for a
useful prognostic model is typically 0.65 to 0.85. The initial c-statistic calculated (prior to
internal validation, see below in section 6.2.9) is known as the apparent c-statistic.

6.2.9 Internal validation

During model development, there is a risk of overfitting (see explanation in section 6.2.5,
page 120) so that the model appears better than it should be. Internal validation serves to give
a less biased estimate of model performance, using only the dataset used to develop the
model. Bootstrapping is the preferred method for internal validation (218). A bootstrap
sample is a random sample, drawn with replacement from the original study sample.
Replacement mimics a random component, making bootstrap samples similar to, but not
identical to the original study sample. Bootstrapping is based on the theory that if you sample
over and over again, the data should approximate true population data. This is achieved by
repeating the entire modelling process with variable selection of 500 bootstrap samples to
replace values from the original sample. Bootstrap adjusted performance, known as bias
corrected c-statistic, better reflects what can be expected when the model is tested or applied
in new individuals from the same underlying source population.

6.2.10 Nomograms and UC Escalation of Therapy Calculator

A nomogram is a graphical representation of a mathematical regression formula that allows
individualised risk prediction to be developed, based on the final logistic regression model.
The prediction rule from TrueColours UC consisted of a total score that corresponded with
the probability that a clinic visit would result in escalation of therapy. Because this might be
unfamiliar to potential users, instructions on how to use the nomogram were included. To
simplify the scoring system, a tabulated system (from this point forward known as the UC
Escalation of Therapy Calculator) was also developed by converting regression coefficients
to easy-to-sum integers, for each predictor used in the final models. The total score (sum of
the integers) related to the outcome probability of escalation of therapy. For nomograms, there is no recommended threshold as to what probability cut-off to use in the clinical setting. Some hospitals may decide to use 0.25, others 0.5 and others 0.75. Safety needs to be considered: missing patients that need escalation of therapy could lead to harm. At a higher cut-off point (eg 0.5 compared to 0.25), the score will identify fewer patients who need to be seen, but will miss more patients who need escalation of therapy. Consequently, three cut-off points were arbitrarily chosen (0.5, 0.25 and 0.1) to examine their sensitivity, specificity, positive- and negative-predictive values against actual clinical decisions made during the outpatient appointments. The details of every patient who had escalation of therapy despite the model predicting that they would not, were examined.
6.3 Results

6.3.1 Demographics

All hospital medical files of the 66 patients in the TrueColours UC pilot were examined. Demographic data can be found in Chapter 4, Table 4-2, page 85. Because five patients withdrew from the study in the first few days after enrolment, only 61 patients had hospital visits during the 6 month pilot. The median (IQR) number of hospital visits per patient was 3 (1, 4). In this development cohort, there were data from 208 outpatient appointments of which 62 resulted in escalation of therapy (Figure 6-1). There were two documented episodes of de-escalations of therapy. Both were to decrease prednisolone dose for patients on a documented reducing regime (patients were already aware of this decrease prior to the appointment).

Figure 6-1: Flow diagram for outcome assessment in the TrueColours UC pilot
FCal = IBDox® faecal calprotectin, Hb = Haemoglobin, WCC = white cell count, Plt = platelets, CRP = C reactive protein, Alb = albumin

Many outpatient appointments occurred when patients were in remission (SCCAI=0,1,2) with a good QoL (IBD Control-8 ≥14). Table 6-1 categorises the SCCAI (as per previously explained thresholds (see section 2.2.11, page 31) at the time of the outpatient appointment into Remission (0,1,2), Mild (3,4,5), Moderate (6,7,8,9,10,11) and Severe (≥12), showing the percentage of patients in each group who received escalation of therapy compared to those who did not receive escalation of therapy. Table 6-2 displays the detail. A SCCAI ≥8 was associated with escalation of therapy in all cases (Figure 6-2).

Table 6-1: Escalation vs no escalation of therapy as categorised by disease activity

<table>
<thead>
<tr>
<th>SCCAI</th>
<th>Remission (0,1,2)</th>
<th>Mild (3,4,5)</th>
<th>Moderate (6,7,8,9,10,11)</th>
<th>Severe (≥12)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escalation n (%)</td>
<td>5 (5%)</td>
<td>21 (33%)</td>
<td>32 (84%)</td>
<td>4 (100%)</td>
<td>62</td>
</tr>
<tr>
<td>No escalation n (%)</td>
<td>98 (95%)</td>
<td>42 (67%)</td>
<td>6 (16%)</td>
<td>0</td>
<td>146</td>
</tr>
<tr>
<td>Total</td>
<td>103</td>
<td>63</td>
<td>38</td>
<td>4</td>
<td>208</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index, No escalation = no increase in medical therapy was prescribed at the outpatient appointment, Escalation = an increase in medical therapy was prescribed at the outpatient appointment.

Table 6-2: Escalation vs no escalation of therapy as categorised by SCCAI

<table>
<thead>
<tr>
<th>SCCAI</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>Total</th>
</tr>
</thead>
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<td>Escalation</td>
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<td></td>
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<td>8</td>
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<td>4</td>
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<td></td>
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<td>1</td>
<td>4</td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>No Escalation</td>
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</tr>
<tr>
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<td>9</td>
<td>15</td>
<td>7</td>
<td>2</td>
<td>4</td>
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<td>Severe</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index
Figure 6-2: Escalation of therapy by SCCAI

SCCAI=Simple Clinical Colitis Activity Index
Table 6-3 categorises need for escalation of therapy compared to IBD Control-8. An IBD Control-8 ≤3 was associated with escalation of therapy in all cases (Figure 6-3).

Table 6-3: Escalation vs no escalation of therapy as categorised by IBD Control-8

<table>
<thead>
<tr>
<th>IBD Control-8</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
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<th>13</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Escalation</td>
<td>5</td>
<td>7</td>
<td>4</td>
<td>6</td>
<td>13</td>
<td>3</td>
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<td>6</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
<td>62</td>
</tr>
<tr>
<td>No escalation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>6</td>
<td>16</td>
<td>11</td>
<td>19</td>
<td>14</td>
<td>47</td>
<td>146</td>
</tr>
</tbody>
</table>

Figure 6-3: Escalation of therapy by IBD Control-8
6.3.2 Model specification

The 10 candidate predictors (described above, section 6.2.4) were used to create a prediction model. Table 6-4 shows median (IQR) values and percentage of missing data for each predictor. 62 hospital clinic visits resulted in escalation of therapy. With 10 predictors, this resulted in an EPV of 6.2.

Table 6-4: Association between each predictor and outcome (escalation vs no escalation of therapy)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Outpatient appointment with escalation (n=62)</th>
<th>Outpatient appointment without escalation (n=146)</th>
<th>Univariate Odds Ratio (95% CI)</th>
<th>Multivariable Odds Ratio (95% CI)</th>
<th>Missing data (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCAI</td>
<td>6 (4, 8)</td>
<td>2 (0, 3)</td>
<td>2.26 (1.84 to 2.89)</td>
<td>1.68 (1.14 to 2.70)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>IBD Control-8</td>
<td>5 (3, 10)</td>
<td>14 (11, 16)</td>
<td>0.7 (0.63 to 0.77)</td>
<td>0.90 (0.71 to 1.12)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>FCal</td>
<td>130 (37, 342)</td>
<td>732 (503, 864)</td>
<td>1.00 (1.00 to 1.01)</td>
<td>1.00 (1.00 to 1.01)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Hb</td>
<td>133 (126, 142)</td>
<td>138 (131, 145)</td>
<td>0.96 (0.93 to 0.98)</td>
<td>1.00 (0.93 to 1.07)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>WCC</td>
<td>7.09 (6.40, 10.36)</td>
<td>6.29 (4.93, 7.82)</td>
<td>1.28 (1.14 to 1.45)</td>
<td>1.01 (0.67 to 1.67)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Pt</td>
<td>299.5 (225, 345)</td>
<td>273.5 (241, 351)</td>
<td>1.00 (0.99 to 1.01)</td>
<td>0.98 (0.97 to 1.00)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>CRP</td>
<td>1.05 (0.5, 2.5)</td>
<td>4 (0.68, 16.8)</td>
<td>1.07 (1.03 to 1.12)</td>
<td>1.00 (0.96 to 1.11)</td>
<td>21 (10)</td>
</tr>
<tr>
<td>Alb</td>
<td>40 (38, 42)</td>
<td>38 (34, 39)</td>
<td>0.83 (0.76 to 0.90)</td>
<td>1.06 (0.86 to 1.32)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Transferrin</td>
<td>24 (17, 37)</td>
<td>32 (24, 42)</td>
<td>0.98 (0.96 to 1.01)</td>
<td>0.98 (0.93 to 1.03)</td>
<td>40 (19)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>61.25 (28.3, 151)</td>
<td>56.1 (21.8, 95.5)</td>
<td>1.002 (1.00 to 1.01)</td>
<td>1.00 (1.00 to 1.02)</td>
<td>39 (19)</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index: scores range 0 (best) to 19 (worst), IBD Control-8: scores range 0 (worst) to 16 (best), FCal=Faecal Calprotectin, Hb=Haemoglobin (g/dL), WCC=white cell count (10^9/L), Pt=platelets (10^9/L), CRP=C-reactive protein (mg/L), Alb=albumin (g/L), transferrin saturation (%), ferritin (mcg/L)

When all 10 predictors were included in the backwards elimination model using the AIC criteria (equivalent to p=0.157) as the pre-specified stopping rule, four significant predictors were identified: SCCAI, IBD Control-8, FCal and Pt.
6.3.3 Model performance

6.3.3.1 SCCAI, IBD Control-8, FCal and Plt

The calibration plot for all four significant predictors (SCCAI, IBD Control-8, FCal and Plt) is shown (Figure 6-4). For this model, the calibration intercept is -0.02 (95% CI -0.53 to 0.48) and the calibration slope 1.12 (0.8 to 1.45). The apparent c-statistic was 0.96 (95% CI 0.92 to 0.98) with a bias-corrected c-statistic of 0.94.

Figure 6-4: Calibration plot for SCCAI, IBD Control-8, FCal and Plt prediction model

SCCAI = Simple Clinical Colitis Activity Index, FCal = IBDoc® Faecal Calprotectin, Plt = platelets (10⁹/L)
6.3.3.2 Additional models

Calibration plots for additional models using less information (and therefore more practical in the clinical setting) were created.

These included

- SCCAI alone (Figure 6-5)
- IBD Control-8 alone (Figure 6-6)
- SCCAI plus IBD Control-8 (Figure 6-7), and
- SCCAI plus IBD Control-8 plus FCal (Figure 6-8).

In clinical practice, recent blood tests are often not available prior to an outpatient appointment and therefore, for reasons of practicality, it was decided that the additional models chosen would not include platelets.
### 6.3.3.2.1 SCCAI alone

When SCCAI alone was used for prediction of escalation, the calibration intercept was -0.00 (95% CI -0.41 to 0.41) and the calibration slope 1.00 (95% CI 0.72 to 1.28). The apparent c-statistic decreased to 0.90 (95% CI 0.84 to 0.94) with a bias-corrected c-statistic of 0.90 (Figure 6-5).

**Figure 6-5: Calibration plot for SCCAI prediction model**

SCCAI = Simple Clinical Colitis Activity Index
6.3.3.2.2 IBD Control-8 alone

When IBD Control-8 alone was used for prediction of escalation, the calibration intercept was 0.00 (95% CI -0.38 to 0.38) and the calibration slope 1.00 (95% CI 0.77 to 1.25). The apparent c-statistic decreased to 0.86 (95% CI 0.84 to 0.94) with a bias-corrected c-statistic of 0.86 (Figure 6-6).

Figure 6-6: Calibration plot for IBD Control-8 prediction model
6.3.3.2.3 SCCAI and IBD Control-8

When SCCAI and IBD Control-8 were combined in a model, the calibration intercept was -0.00 (95% -0.42 to 0.42), calibration slope 1.00 (95% 0.73 to 1.27), apparent c-statistic 0.90 (95% 0.84 to 0.94) with a bias-corrected c-statistic of 0.90 (Figure 6-7).

Figure 6-7: Calibration plot for SCCAI and IBD Control-8 prediction model

SCCAI = Simple Clinical Colitis Activity Index
6.3.3.2.4 SCCAI, IBD Control-8 and FCal

When SCCAI, IBD Control-8 and FCal were combined in a model, the calibration intercept was 0.01 (95% -0.47 to 0.48), slope 1.09 (95% 0.78 to 1.40), apparent c-statistic 0.95 (95% 0.91 to 0.97) with a bias-corrected c-statistic of 0.94 (Figure 6-8).

Figure 6-8: Calibration plot for SCCAI, IBD Control-8 and FCal prediction model

SCCAI = Simple Clinical Colitis Activity Index, FCal = IBDoc Faecal Calprotectin
To provide a summary of the c-statistics of the above models, these are displayed in Table 6-5.

Table 6-5: Summary of prediction models with corresponding bias-corrected c-statistics

<table>
<thead>
<tr>
<th>Model</th>
<th>Bias-corrected c statistic</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD Control-8</td>
<td>0.86</td>
</tr>
<tr>
<td>SCCAI</td>
<td>0.90</td>
</tr>
<tr>
<td>SCCAI plus IBD Control-8</td>
<td>0.90</td>
</tr>
<tr>
<td>SCCAI plus IBD Control-8 plus FCal</td>
<td>0.94</td>
</tr>
<tr>
<td>SCCAI plus IBD Control-8 plus PCal plus Plts</td>
<td>0.94</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index, FCal = IBDoc® Faecal Calprotectin, Plt = platelets

To provide full transparency for each of the four models developed, the regression coefficients and intercepts are shown in Table 6-6. These are the values that relate to the 

\[ \text{logit (p)} = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + \ldots + b_kX_k \]

equation (section 6.2.7, page 120). For example, using the SCCAI alone model: if the SCCAI was 3, using the table below, logit (p) = -3.8944 + 0.7840 x 3.

Table 6-6: Regression coefficients and intercepts for prediction models

<table>
<thead>
<tr>
<th>Regression coefficients of predictors</th>
<th>SCCAI alone</th>
<th>IBD Control-8 alone</th>
<th>SCCAI and IBD Control-8</th>
<th>SCCAI, IBD Control-8 and FCal</th>
<th>SCCAI, IBD Control-8, FCal and Plts</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCAI Coef (S.E)</td>
<td>0.7840 (0.1101)</td>
<td></td>
<td>0.6192 (1344)</td>
<td>0.5798 (0.0002)</td>
<td>0.5883 (0.1709)</td>
</tr>
<tr>
<td>IBD Control-8 Coef (S.E)</td>
<td>-0.3562 (.00530)</td>
<td>-0.1289 (0.0670)</td>
<td>-0.1385 (0.0753)</td>
<td>-0.1613 (0.0876)</td>
<td></td>
</tr>
<tr>
<td>FCal Coef (S.E)</td>
<td></td>
<td></td>
<td>0.0029 (0.0008)</td>
<td>0.0040 (0.0013)</td>
<td></td>
</tr>
<tr>
<td>Plts Coef (S.E)</td>
<td></td>
<td></td>
<td></td>
<td>-0.0126 (0.0051)</td>
<td></td>
</tr>
<tr>
<td>Intercept (S.E)</td>
<td>-3.8944 (0.5033)</td>
<td>2.7055 (1.0077)</td>
<td>-1.9690 (1.0816)</td>
<td>-3.1460 (1.2469)</td>
<td>0.0371 (5.0955)</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index, FCal = IBDoc® faecal calprotection, Coef = regression coefficient, S.E = standard error
6.3.4 Nomograms and UC Escalation of Therapy Calculator

To determine how a prediction model might be used in a real or virtual clinic, nomograms and simplified scoring systems were constructed for some of the models:

- A prediction model combining SCCAI and IBD Control-8
- A prediction model combining SCCAI, IBD Control-8 and FCal
6.3.4.1  Nomogram for prediction model using SCCAI and IBD Control-8

The nomogram and corresponding instructions for the prediction model using SCCAI and IBD Control-8 is shown (Figure 6-9).

**Figure 6-9: Nomogram for SCCAI and IBD Control-8 prediction model**

![Nomogram](image)

**Instructions for use**

1. Plot SCCAI total score on SCCAI line and draw a line UPWARDS to the points scale and record value in box to the right
2. Plot IBD Control-8 total score on IBD Control-8 line and draw a line UPWARDS to the points scale and record value in box to the right
3. Add all points and record in orange box
4. Mark this value on the Total points line
5. Draw a line DOWNWARDS to the Probability of escalation line and enter this number in the blue box
**Working example**

If a patient had an SCCAI of 7 and an IBD Control-8 of 12, this would equal 50 points plus 8 points = 58 points, which corresponds to a probability of escalation of 0.70. The red circles and arrows on the nomogram below show the process of using the nomogram (Figure 6-10).

If the probability of escalation cut-off = 0.5, a probability of 0.7 would qualify for requiring an outpatient appointment.

**Figure 6-10: Working example of the SCCAI and IBD Control-8 nomogram**

![Nomogram Diagram]
6.3.4.2 UC Escalation of Therapy Calculator: SCCAI and IBD Control-8

The simplified scoring system for SCCAI and IBD Control-8 and corresponding instructions are shown below (Figure 6-11).

Figure 6-11: UC Escalation of Therapy Calculator for SCCAI and IBD Control-8

<table>
<thead>
<tr>
<th>SCCAI</th>
<th>Points</th>
<th>+</th>
<th>IBD CONTROL</th>
<th>Points</th>
<th>= TOTAL POINTS</th>
<th>Probability of Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td></td>
<td>0</td>
<td>24</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td></td>
<td>1</td>
<td>22</td>
<td>13</td>
<td>0.05</td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td></td>
<td>2</td>
<td>21</td>
<td>34</td>
<td>0.25</td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td></td>
<td>3</td>
<td>20</td>
<td>47</td>
<td>0.50</td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td></td>
<td>4</td>
<td>18</td>
<td>59</td>
<td>0.75</td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td></td>
<td>5</td>
<td>16</td>
<td>80</td>
<td>0.95</td>
</tr>
<tr>
<td>6</td>
<td>43</td>
<td></td>
<td>6</td>
<td>15</td>
<td>100</td>
<td>0.99</td>
</tr>
<tr>
<td>7</td>
<td>50</td>
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<td>7</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td></td>
<td>8</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td></td>
<td>9</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>71</td>
<td></td>
<td>10</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>79</td>
<td></td>
<td>11</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>86</td>
<td></td>
<td>12</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>93</td>
<td></td>
<td>13</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥14</td>
<td>100</td>
<td></td>
<td>14</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16</td>
<td>0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Instructions for use

1. For each box, please circle the score and corresponding points
2. Add up the two points to get the total points
3. Correspond the total points with the probability of escalation

Working example

If a patient had a SCCAI of 4 and an IBD Control-8 of 12, they would get 29 points plus 6 points = 35 total points which corresponds to a probability of escalation of approximately 0.25
6.3.4.3 Nomogram for prediction model using SCCAI, IBD Control-8 and FCal

The nomogram and corresponding instructions for a prediction model for SCCAI, IBD Control-8 and FCal is shown (Figure 6-12).

Figure 6-12: Nomogram for SCCAI, IBD Control-8 and FCal prediction model

Instructions for use

1. Plot SCCAI total score on SCCAI line and draw a line UPWARDS to points scale and record value in box to the right

2. Plot IBD Control-8 total score on IBD Control-8 line and draw a line UPWARDS to points scale and record value in box to the right

3. Plot FCal result on the calprotectin line and draw a line UPWARDS to Points scale and record value in box to the right

4. Add all points and record in box labelled Total points

5. Mark this value on the Total points line

6. Draw a line vertically DOWNWARDS to find probability of requiring escalation of therapy
6.3.4.4 UC Escalation of Therapy Calculator: SCCAI, IBD Control-8 and FCAl

The simplified scoring system for SCCAI, IBD Control-8 and FCAl with corresponding instructions are shown below (Figure 6-13).

**Figure 6-13: UC Escalation of Therapy Calculator for SCCAI, IBD Control-8 and FCAl**

<table>
<thead>
<tr>
<th>SCAAI</th>
<th>Points</th>
<th>+</th>
<th>IBD CONTROL</th>
<th>Points</th>
<th>+</th>
<th>CalPro</th>
<th>Points</th>
<th>= TOTAL POINTS</th>
<th>Probability of Escalation</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td></td>
<td>24</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.01</td>
</tr>
<tr>
<td>1</td>
<td>7</td>
<td></td>
<td>22</td>
<td>100</td>
<td></td>
<td>4</td>
<td>13</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>14</td>
<td></td>
<td>21</td>
<td>200</td>
<td></td>
<td>7</td>
<td>34</td>
<td>0.25</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21</td>
<td></td>
<td>20</td>
<td>300</td>
<td></td>
<td>11</td>
<td>47</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>29</td>
<td></td>
<td>18</td>
<td>400</td>
<td></td>
<td>14</td>
<td>59</td>
<td>0.75</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>36</td>
<td></td>
<td>16</td>
<td>500</td>
<td></td>
<td>18</td>
<td>80</td>
<td>0.95</td>
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</tr>
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<td>6</td>
<td>43</td>
<td></td>
<td>15</td>
<td>600</td>
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<td>0.99</td>
<td></td>
</tr>
<tr>
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<td>50</td>
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<td>14</td>
<td>700</td>
<td></td>
<td>25</td>
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<tr>
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<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>79</td>
<td></td>
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<td>1100</td>
<td></td>
<td>40</td>
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<td>1300</td>
<td></td>
<td>47</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥14</td>
<td>100</td>
<td></td>
<td>3</td>
<td>1400</td>
<td></td>
<td>50</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2</td>
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<td>58</td>
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<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>1700</td>
<td></td>
<td>61</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1800</td>
<td></td>
<td>65</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1900</td>
<td></td>
<td>68</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2000</td>
<td></td>
<td>72</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Instructions for use**

1. For each box, please circle the score and points
2. Add up all three points to get the total points
3. Correspond the total points with the probability of escalation
6.3.4.5 Effect of using different cut-offs for probability of escalation

Different cut-offs for probability of escalation of therapy were examined. Using the SCCAI, IBD Control-8 and FCal prediction model as an example, cut-offs of 0.5, 0.25 and 0.1 were compared to explore the optimal cut-off for clinical practice (Table 6-7, Table 6-9, and Table 6-11).

6.3.4.5.1 Probability of escalation of therapy when cut-off = 0.5

Table 6-7: Escalation of therapy when cut-off probability = 0.5 in the TrueColours UC pilot

<table>
<thead>
<tr>
<th>Probability from the model</th>
<th>Escalation of therapy</th>
<th>No escalation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted probability &lt;0.5</td>
<td>16</td>
<td>141</td>
</tr>
<tr>
<td>Predicted probability ≥0.5</td>
<td>46</td>
<td>5</td>
</tr>
</tbody>
</table>

Using this model, 46/62 escalations at outpatient appointments were correctly identified, whilst 5/146 non-escalations were incorrectly identified as escalations (sensitivity 74%, specificity 97%, positive-prediction value 90% and negative-prediction value 90%). Importantly 16 patients had had treatment escalated when their prediction probability was <0.5. The escalations included prescription of 5-ASA suppositories (n=11), oral 5-ASA (n=2), oral prednisolone (n=1), mercaptopurine (n=1), or vedolizumab (n=1) (Table 6-8).
Table 6-8: Missed escalation decisions when cut-off probability = 0.5 for the SCCAI, IBD Control-8, FCal prediction model

<table>
<thead>
<tr>
<th>Patient</th>
<th>SCCAI</th>
<th>IBD Control-8</th>
<th>FCal</th>
<th>Hb</th>
<th>WCC</th>
<th>Plt</th>
<th>CRP</th>
<th>Alb</th>
<th>Predicted Probability</th>
<th>Escalation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>16</td>
<td>504</td>
<td>133</td>
<td>9</td>
<td>319</td>
<td>2.8</td>
<td>39</td>
<td>0.02</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>16</td>
<td>500</td>
<td>146</td>
<td>4.7</td>
<td>197</td>
<td>0.2</td>
<td>40</td>
<td>0.03</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>11</td>
<td>25</td>
<td>156</td>
<td>6</td>
<td>133</td>
<td>6.0</td>
<td>39</td>
<td>0.09</td>
<td>vedolizumab</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>10</td>
<td>135</td>
<td>139</td>
<td>8.43</td>
<td>319</td>
<td>2.5</td>
<td>41</td>
<td>0.14</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>15</td>
<td>851</td>
<td>149</td>
<td>7</td>
<td>225</td>
<td>3.1</td>
<td>40</td>
<td>0.17</td>
<td>mercaptopurine</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>14</td>
<td>817</td>
<td>138</td>
<td>7.2</td>
<td>300</td>
<td>5.3</td>
<td>35</td>
<td>0.18</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
<td>6</td>
<td>259</td>
<td>127</td>
<td>2.2</td>
<td>148</td>
<td>0.5</td>
<td>40</td>
<td>0.29</td>
<td>5-ASA oral</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
<td>11</td>
<td>M</td>
<td>137</td>
<td>7.1</td>
<td>338</td>
<td>6.0</td>
<td>39</td>
<td>0.34</td>
<td>prednisolone</td>
</tr>
<tr>
<td>9</td>
<td>4</td>
<td>16</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
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<td>6</td>
<td>11</td>
<td>214</td>
<td>129</td>
<td>5.3</td>
<td>255</td>
<td>0.7</td>
<td>37</td>
<td>0.36</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>11</td>
<td>6</td>
<td>10</td>
<td>256</td>
<td>142</td>
<td>5</td>
<td>225</td>
<td>5.6</td>
<td>38</td>
<td>0.42</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>12</td>
<td>2</td>
<td>8</td>
<td>M</td>
<td>148</td>
<td>7.0</td>
<td>206</td>
<td>0.4</td>
<td>41</td>
<td>0.44</td>
<td>5-ASA oral</td>
</tr>
<tr>
<td>13</td>
<td>4</td>
<td>13</td>
<td>858</td>
<td>149</td>
<td>7</td>
<td>225</td>
<td>31</td>
<td>40</td>
<td>0.47</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>14</td>
<td>4</td>
<td>12</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>M</td>
<td>0.48</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>15</td>
<td>5</td>
<td>2</td>
<td>160</td>
<td>158</td>
<td>5.7</td>
<td>146</td>
<td>2.4</td>
<td>39</td>
<td>0.49</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>16</td>
<td>4</td>
<td>11</td>
<td>M</td>
<td>124</td>
<td>6.7</td>
<td>124</td>
<td>0.3</td>
<td>36</td>
<td>0.49</td>
<td>5-ASA suppository</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index: scores range 0 (best) to 19 (worst), IBD Control-8: scores range 0 (worst) to 16 (best), FCal = IBDoc faecal calprotectin, Hb = Haemoglobin (g/dL), WCC = white cell count (10^9/L), Plt = platelets (10^9/L), CRP = C-reactive protein (mg/L), Alb = albumin (g/L), Predicted probability = predicted probability of escalation, Escalation of therapy = medical therapy that was prescribed at the outpatient appointment
6.3.4.5.2 Probability of escalation of therapy when cut-off = 0.25

Table 6-9: Escalation of therapy when cut-off probability = 0.25 in the TrueColours UC pilot

<table>
<thead>
<tr>
<th>Probability from the model</th>
<th>Escalation of therapy</th>
<th>No escalation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predicted probability &lt;0.25</td>
<td>6</td>
<td>119</td>
</tr>
<tr>
<td>Predicted probability ≥0.25</td>
<td>56</td>
<td>27</td>
</tr>
</tbody>
</table>

Using this model, 56/62 escalations at outpatient appointments were correctly identified, whilst 27/146 of non-escalations were incorrectly identified as escalations (sensitivity of 90%, specificity of 82%, positive predictive value of 67% and negative predictive value of 95%). 6 patients had treatment escalated when their prediction probability was <0.25. The escalations included 5-ASA suppositories (n=4), mercaptopurine (n=1), or vedolizumab (n=1) (Table 6-10).

Table 6-10: Missed escalation decisions when probability cut-off = 0.25 for the SCCAI, IBD Control-8, FCal prediction model

<table>
<thead>
<tr>
<th>Patient</th>
<th>SCCAI</th>
<th>IBD Control-8</th>
<th>FCal</th>
<th>Hb</th>
<th>WCC</th>
<th>Plt</th>
<th>CRP</th>
<th>Alb</th>
<th>Predicted Probability</th>
<th>Escalation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>16</td>
<td>504</td>
<td>133</td>
<td>9</td>
<td>319</td>
<td>2.8</td>
<td>39</td>
<td>0.02</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>16</td>
<td>500</td>
<td>146</td>
<td>4.7</td>
<td>197</td>
<td>0.2</td>
<td>40</td>
<td>0.03</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>11</td>
<td>25</td>
<td>156</td>
<td>6</td>
<td>133</td>
<td>6.0</td>
<td>39</td>
<td>0.09</td>
<td>vedolizumab</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
<td>10</td>
<td>135</td>
<td>139</td>
<td>8.43</td>
<td>319</td>
<td>2.5</td>
<td>41</td>
<td>0.14</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>15</td>
<td>851</td>
<td>149</td>
<td>7</td>
<td>225</td>
<td>3.1</td>
<td>40</td>
<td>0.17</td>
<td>mercaptopurine</td>
</tr>
<tr>
<td>6</td>
<td>2</td>
<td>14</td>
<td>817</td>
<td>138</td>
<td>7.2</td>
<td>300</td>
<td>5.3</td>
<td>35</td>
<td>0.18</td>
<td>5-ASA suppository</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index: scores range 0 (best) to 19 (worst), IBD Control-8: scores range 0 (worst) to 16(best), FCal = IB Doc® faecal Calprotectin, Hb = Haemoglobin (g/dL), WCC = white cell count (10⁹/L), Plt = platelets (10⁹/L), CRP = C-reactive protein (mg/L), Alb = albumin (g/L), Predicted probability = predicted probability of escalation, Escalation of therapy = medical therapy that was prescribed at the outpatient appointment
6.3.4.5.3 Probability of escalation of therapy when cut-off = 0.1

Table 6-11: Escalation of therapy when cut-off probability = 0.1 in the TrueColours UC pilot

<table>
<thead>
<tr>
<th>Predicted probability &lt;0.1</th>
<th>Escalation of therapy</th>
<th>No escalation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3</td>
<td>104</td>
</tr>
<tr>
<td>Predicted probability ≥0.1</td>
<td>59</td>
<td>42</td>
</tr>
</tbody>
</table>

Using this model, 59/62 escalations at outpatient appointments were correctly identified, whilst 42/146 of non-escalations were incorrectly identified as escalations (sensitivity of 95%, specificity of 71%, positive predictive value of 58%, negative predictive value of 97%). 3 patients had treatment escalated when their prediction probability was <0.1. The escalations included 5-ASA suppositories (n=2) or vedolizumab (n=1) (Table 6-12). The patient for whom vedolizumab was prescribed had been considering commencing vedolizumab for some time and this decision was not based on symptomatology but on recent endoscopic results and need for recurrent courses of oral prednisolone.

Table 6-12: Missed escalation decisions when probability cut-off = 0.1 for the SCCAI, IBD Control-8, FCal prediction model

<table>
<thead>
<tr>
<th>Patient</th>
<th>SCCAI</th>
<th>IBD Control-8</th>
<th>FCal</th>
<th>Hb</th>
<th>WCC</th>
<th>Plt</th>
<th>CRP</th>
<th>Alb</th>
<th>Predicted Probability</th>
<th>Escalation of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>16</td>
<td>504</td>
<td>133</td>
<td>9</td>
<td>319</td>
<td>2.8</td>
<td>39</td>
<td>0.02</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>16</td>
<td>500</td>
<td>146</td>
<td>4.7</td>
<td>197</td>
<td>0.2</td>
<td>40</td>
<td>0.03</td>
<td>5-ASA suppository</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>11</td>
<td>25</td>
<td>156</td>
<td>6</td>
<td>133</td>
<td>6.0</td>
<td>39</td>
<td>0.09</td>
<td>vedolizumab</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index: scores range 0 (best) to 19 (worst), IBD Control-8: scores range 0 (worst) to 16(best), FCal = IBDoc faecal calprotectin, Hb = Haemoglobin (g/dL), WCC= white cell count (10⁹/L), Plt = platelets (10⁹/L), CRP = C-reactive protein (mg/L), Alb = albumin (g/L), Predicted probability = predicted probability of escalation, Escalation of therapy = medical therapy that was prescribed at the outpatient appointment
6.4 Discussion

The aim of this work was to determine whether remote real time entry of PROMs through TrueColours UC could be incorporated into a single prediction score to assist with identifying which patients with UC were more likely to receive escalation of therapy if they attended an outpatient appointment. For prediction of escalation of therapy, it appears that no similar model exists in the IBD field, either in the UK or internationally.

For the escalation of therapy prediction models described in this chapter, symptoms proved to be the most powerful predictor (SCCAI model bias-corrected c-statistic 0.90). This makes sense, as the SCCAI descriptors (bowel frequency, nocturnal bowel frequency, urgency, bleeding, general well-being and extraintestinal manifestations), which patients were prompted to submit through TrueColours UC closely align with what is asked at an outpatient appointment. The point is that if this information, which can be filled in remotely by the patient, can accurately predict the outcome of an outpatient appointment (in terms of escalation of therapy), it has the potential to improve resource utilisation. The preliminary analysis of the TrueColours UC data showed that only 5% of patients in remission and 9% with an IBD-Control ≥12 required escalation of therapy.

Prediction modelling, including all 10 variables collected on TrueColours UC independently showed that the symptoms (predominantly the SCCAI) predicted whether escalation of therapy was needed. The model with the overall best performance were the combination of SCCAI, IBD Control-8, FCal and Plt (bias-corrected c-statistic 0.94). Other models including SCCAI alone, IBD Control-8 alone, SCCAI plus IBD Control-8, and SCCAI, IBD Control-8 and FCal were explored and although slightly inferior to the full model, all had good performance. For practical reasons, it was decided to only further develop two models into
nomograms and UC Escalation of Therapy calculators. These two models were SCCAI plus IBD Control-8 and SCCAI, IBD-Control-8 and FCal. Although SCCAI alone provided an adequate prediction model, the addition of IBD Control-8 and FCal did contribute information which further refined the probability of escalation of therapy. Including these predictors decreased the chance of patients who required escalation of therapy being missed. This is most likely to be useful in those patients where disease activity is borderline (eg SCCAI total score of 3-5).

The choice of which model to use in the clinical setting will depend on what information is available. For example, if the only SCCAI and IBD Control-8 information were available, this information could be used. However, if a recent FCal was also available, the prediction model including FCal would improve accuracy (especially in those patients who may be borderline). Adding platelets slightly improved prediction, but probably not enough to justify asking patients to have an additional blood test.

These models have been developed in a single UC population. Although this population is representative of the overall UC population in Oxford (Chapter 3, section 3.3.2.1, page 64) there has been no external validation either within Oxford or elsewhere. External validation (testing in a separate cohort) is essential prior to implementation of this prediction score. If this validation was successful, an algorithm could be incorporated into TrueColours UC to allow automatic notification whether a patient was likely to require escalation of therapy. It does not indicate what escalation is needed however would alert both the patient and the treating team that communication needed to occur. This highlights the issue of whether a de-escalation calculator is also required. In this pilot, there were only two de-escalations documented, and in both cases the patients were already aware of the instructions, however de-escalation needs to be further examined in other cohorts.
The choice of which cut-off to use for the probability of escalation is important. Missed escalations for the three different cut-off levels (0.5, 0.25 and 0.1) revealed that most of missed escalations were for 5-ASA suppositories. For safety reasons, it may be best initially to implement a lower probability of escalation cut-off (eg 0.1). This would still achieve the desired aim of improving resource utilisation by over 50%. A proportion of patients who do not require escalation (false positives) would still be seen however very few patients would be missed. On the contrary, if a level of 0.5 was chosen as the cut-off, more patients requiring escalation would be missed, although it would mean that fewer overall patients would need to be seen.

AmbuFlex (161) is the best example of how PROMs have improved resource utilisation. Although AmbuFlex has not been implemented for IBD, it has been used for successfully for other chronic diseases. Instead of an algorithm that would require a threshold for each question within each PROM to be decided upon, a prediction score could be used to replicate this process. As with AmbuFlex, non-adherence to electronic capture of these PROMs would generate a clinic appointment.

There are other reasons for outpatient appointments besides treatment escalation, for example to arrange surveillance colonoscopy or pregnancy planning. There is an argument that by not seeing patients as frequently, there may be medical problems not covered by the PROMs or missed opportunities for patient education and preventative healthcare opportunities. However, there is also a counter argument that if the outpatient appointments are pushed to capacity by seeing patients in remission, that those with active (mild, moderate and severe)
disease often have delays in treatment. An annual phone clinic with checklist or integrated questionnaire within TrueColours UC to cover these possibilities would need to be instituted. Also, like with AmbuFlex, this system would need to allow patients to overrule the automated decision if they wished. In Denmark, it was initially perceived that patients would prefer face-to-face appointments even if they were well, but only 23% of patients with epilepsy overruled the automated decision. Qualitative interviews performed in the TrueColours UC cohort indicated that a system such as described above would be preferable as compared to the current appointment scheduling (Chapter 5, section 5.3.6, page 108). If TrueColours UC prediction scores were implemented into clinical practice, safety and outcomes would need to be monitored.

The feasibility of implementing this prediction score in the clinic setting also needs to be considered. If potentially half of the visits may be replaced by a less resource demanding activity, there may be an economic argument for a shift to optimising outpatient appointments. The Danish government initiated an analysis which has demonstrated a positive national business case and considerable quality gain (228). There has subsequently been an agreement for nationwide implementation in three diagnostic groups, before 2020. Further progress has also been made with the recent publication of the protocol for a randomised trial comparing Ambuflex at fixed intervals (Standard Ambuflex) vs patient-initiated Ambuflle in outpatients with epilepsy (229).

An important limitation of the prediction models suggested above is that escalation of therapy is somewhat subjective as the decision regarding escalation will be dependent on which doctor was seen, especially in the case of mild disease. This study included any escalation, no matter how small, to ensure that all events were captured. It would be difficult to define
escalation in any other way as there will always be differences in medical practice, even within physicians working in the same clinic. There is also the possibility that retrospective review of the medical notes may have missed escalation of therapy if these changes were not documented correctly by the treating doctor.

To summarise, real time remote data entry through TrueColours UC was used to create models that predicted whether escalation of therapy was likely if a patient were to attend an outpatient appointment. Symptoms, all of which were entered remotely, were the dominant driver of need for escalation of therapy. These prediction models need to be externally validated, however certainly have the potential to improve outpatient clinic resource utilisation.
7 Chapter Seven

Analysis of real time longitudinal TrueColours Ulcerative Colitis data

7.1 Introduction

Robust, data-rich longitudinal records present enormous opportunities. The amount of data being digitally collected and stored is vast and expanding. As a result, the science of data management and analysis is also advancing, allowing exploration of previously unknown or unmeasurable information.

In this thesis, longitudinal data refers to the collection of repeated measurements over the 6 month pilot. The repeated measurements are those variables collected by TrueColours UC: daily symptoms (SCCAI), fortnightly QoL (IBD Control-8, CUCQ-8 and EQ-5D), monthly faecal calprotectin (FCal), monthly bloods (Hb, WCC, Plts, Alb, CRP, transferrin saturations and ferritin), 6 monthly endoscopy (UCEIS) and histopathology (Nancy index) (see Chapter 2, section 2.3.6, 2.3.11, and 2.3.12).

There are no publications describing analysis of this type of longitudinal data in IBD. To draw an analogy from another chronic disease, analysis of longitudinal electronically collected data has been performed in psychiatry. Tsanas et al. (230) studied patients with bipolar disorder (n=48), borderline personality disorder (n=51) and healthy controls (n=51). Five questionnaires were collected. Mood Zoom (MZ), which is a novel daily clinical questionnaire used for mood monitoring, was completed daily as part of a smartphone application. The other four questionnaires (Altman Self Rating Mania scale (ASRM), Quick Inventory of Depressive Symptomatology (QIDS), Generalised Anxiety Disorder-7 (GAD-7)
and EQ-5D (EuroQoL), were submitted on a weekly basis using the TrueColours platform. Each questionnaire had between 5 to 9 descriptors, which led to almost 400,000 repeated measurements. Results showed that the daily MZ correlated well with the weekly QIDS, GAD-7 and EQ-5D (correlation coefficient >0.5, p<0.0001). Compared to healthy controls, bipolar disorder and borderline personality disorder participants exhibited different trends and variability. Patients had higher self-reported scores in mania, depression and anxiety as well as lower QoL. Analysis of daily MZ variability showed that it could differentiate between bipolar disorder and borderline personality disorder, with irritability being the crucial differentiating factor. This differentiation was not possible using weekly questionnaires.

New mathematical models to analyse longitudinal data are being explored. As an example, Kormilitzin et al (231) analysed mood data from CEQUEL (Comparative Evaluation of Quetiapine-Lamotrigine combination versus quietapine monotherapy in people with bipolar depression), a double blind randomised placebo controlled trial (232). 29 patients self-reported the QIDS weekly for 12 weeks using the TrueColours platform. Rather than analysing the change in the QIDS total score, the analysis focused on the delays, defined as the time interval between the prompt and the actual response. Delays in responding to text message prompts about depressive symptoms were found to be a novel indicator of treatment effect, with delay patterns appearing to be a more objective correlate of mood.

On an individual basis, real time monitoring affects clinical care (see Chapter 5). At a population level, longitudinal data, comprising multiple repeated measurements can provide insights into questionnaires, disease fluctuation, correlations and outcomes. Applications of
this type of longitudinal data analysis are diverse and growing, and a few examples include studies of addictive behaviours (233) and eating disorders (234).

This thesis only presents the longitudinal data for the TrueColours UC pilot cohort. Nevertheless, it provides insights into what may be possible in the future with a larger cohort over longer periods of time. The reasoning behind the approach taken to explore the TrueColours UC pilot data takes account of clinical symptoms (SCCAI), the impact of scoring extraintestinal manifestations (EIMs) on the SCCAI, the correlation between QoL and symptoms, the impact of data collection frequency, implications for phenotyping, incorporation of flare detection algorithms, and impact of other measures (faecal calprotectin, endoscopy and histopathology).

The SCCAI (103) is a clinical index specific to UC (see Chapter 2, section 2.3.6.1, page 37). Developed in 1998, it did not follow modern criteria for index development, was primarily based on the Powell Tuck index (235), which includes symptoms, physical examination findings and sigmoidoscopy grading. Nocturnal bowel frequency and urgency to defaecation were added and the general well-being score from the Harvey Bradshaw Index (236), an index for Crohn’s disease, replaced the general health question in the Powell-Tuck index. The category of extraintestinal manifestations incorporated arthritis, uveitis, erythema nodosum and pyoderma gangrenosum.

The SCCAI was then devised by determining which five descriptors gave the best correlation with the Powell-Tuck index, with correlation coefficients of 0.959, p < 0.0001 being achieved with the following five descriptors: bowel frequency, nocturnal bowel motions, urgency to defaecation, blood in the stool, and general well-being. Correlation coefficients between each
descriptor and the final SCCAI score were bowel frequency (day) 0.76, bowel frequency (nocturnal) 0.77, urgency 0.8, blood in stool 0.74, general well-being 0.77, and extraintestinal manifestations 0.4. It is unclear why extraintestinal manifestations were included in the SCCAI given the poor correlation. Further validation of the SCCAI was performed through comparison with another UC index, the unvalidated Seo index (237), with a correlation coefficient 0.924, p<0.0001. The SCCAI has not been fully validated, but it is widely used in clinical practice and in clinical trials (238). It remains unclear which descriptors contribute most to the variability of the SCCAI.

The EIMs that were chosen at the time of development of the SCCAI were arthritis, uveitis, erythema nodosum and pyoderma gangrenosum. These EIMs contribute four (one for each of the EIMs included) out of a total of 19 SCCAI points. The relationship between disease activity and EIMs is unclear. While some EIMs (such as erythema nodosum) have traditionally been associated with active disease, others (such as pyoderma gangrenosum) have not. It is increasingly clear that the major determinant of EIMs are genetic rather than due to underlying disease activity (239). For this reason, physicians question whether the presence or absence of EIMs have any place in an index designed to capture disease activity (240). By housing multiple repeat measurements of the SCCAI and its component descriptors, the TrueColours UC data provided the opportunity to explore these relationships.

Correlation between QoL indices and the SCCAI has been performed (111, 113). When IBD Control (Chapter 2, section 2.3.6.2, page 38), an IBD-specific patient-reported outcome measure of QoL, was developed, there was a validation phase which reported moderate to high negative correlation with the SCCAI (correlation coefficient -0.72, p<0.01) (111). The CUCQ-8, (Chapter 2, section 2.3.6.2, page 38), another IBD-specific patient-reported
outcome measure of QoL, found low correlation with the SCCAI (correlation coefficient 0.35, p<0.05) (113). During the development of both the IBD Control and CUCQ-8, validation involved correlation to the EQ-5D, a generic measure of QoL (Chapter 2, 2.3.6.2, page 38). For both indices, there was moderate correlation with the EQ-5D (IBD Control: correlation coefficient 0.68, p<0.001, CUCQ8: correlation coefficient -0.58, p<0.05). Both IBD Control and CUCQ-8 were developed at a similar time, and have never been compared with each other. TrueColours UC data provided the opportunity to correlate the above QoL indices with the SCCAI and with each other.

The optimal frequency for patients to enter real time symptom data in UC is unknown. All IBD e-health programmes have set different frequencies. For example, Constant Care requested monthly input of symptoms when in remission, daily input when relapsing (65), myIBDCoach requested monthly symptom input (54), and for TrueColours UC we requested daily symptom input (see Table 1-1, page 11). More frequent data input must equate with more accurate information about disease fluctuation, however user fatigue must be considered. Access to daily symptom data through TrueColours UC provided an opportunity to determine how much meaningful information is lost when intervals are lengthened.

Access to longitudinal data should allow more accurate phenotyping of patterns of disease. Classifying UC (for example remission vs persistently active vs relapsing pattern) is usually performed retrospectively through examination of medical notes. Clustering patients by disease pattern, represented by the percentage of time spent in each disease category (remission, mild, moderate, severe), may be a more objective way of classifying disease course. Clustering is the task of grouping a set of patients in such a way that patients in the same group (called a cluster) are more similar to each other than to those in other clusters.
Incorporation of a flare detection algorithm may be useful as it would allow time spent in states of disease exacerbation to be better quantified. A similar algorithm has been used to identify episodes of depression and mania using the data collected by TrueColours Bipolar (241). The general algorithm is based on the pre-defined rules (i.e. minimal number of days spent in episodes/flares, the value of a rating scale threshold) and can be adjusted to different rating scales. For example, in TrueColours Bipolar, the identification of episodes of depression was performed using the following rules: at least two consecutive values of $\geq 11$ on the QIDS scale. In the current analysis of TrueColours UC, this algorithmic approach was adopted with corresponding adjustments to the SCCAI.

Determination of disease activity is an essential part of clinical management. The most accurate way to evaluate disease extent and severity is endoscopy, supplemented by biopsy (242). Unfortunately, this is invasive, time consuming, requires a professional operator and is limited by cost (243). Patient symptoms do not reliably reflect the level of disease activity (244). Faecal calprotectin (FCal) has been shown to have moderate correlation with the UCEIS (correlation coefficient 0.607) (244) and histopathology (correlation coefficient 0.521) (245). Published cut-offs for FCal in UC are largely based on prediction of relapse rather than prediction of endoscopic or histopathologic activity (246, 247). During the TrueColours pilot, patients were asked to perform monthly FCals. These data can therefore be used to test the correlation between FCal, symptoms, endoscopy and histopathology and to assist in establishing cut-offs for remission vs active disease.
With access to endoscopic and histopathological results, it is possible to categorise disease activity independently of symptom scores. Correlating a combination of endoscopic and histopathologic definitions of remission and active disease with real time data collection of other variables including symptoms and blood results has not previously been performed.

Each of the above themes are explored in the subsequent methods and results sections. The aim of this chapter is to explore the potential of performing longitudinal analysis on multiple repeated measurements in the UC population.
7.2 Methods

7.2.1 Definitions

For this thesis, index refers to the instrument for assessing activity (for example SCCAI or IBD Control-8), descriptors are the individual items that make up the index (for example rectal bleeding is a descriptor of the SCCAI index), sub-score is the numerical value given to a descriptor, and score is the overall numerical value for an index (for example, a patient may get a score of 10 out of 19 for the SCCAI). The SCCAI descriptors are listed in Table 7-1.

Table 7-1: Simple Colitis Activity Index (SCCAI)

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Scale</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Bowel frequency (day)</td>
<td>0-3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4-6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>7-9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;9</td>
<td>3</td>
</tr>
<tr>
<td>2 Bowel frequency (nocturnal)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4-6</td>
<td>2</td>
</tr>
<tr>
<td>3 Urgency of defecation</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hurry</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Immediately (toilet nearby)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Incontinence</td>
<td>3</td>
</tr>
<tr>
<td>4 Blood in stool</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Trace</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Occasionally frank (&lt;50% of defecation)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Usually frank (&gt;50% of defecation)</td>
<td>3</td>
</tr>
<tr>
<td>5 General well-being</td>
<td>Very well</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Slightly below par</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Poor</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Very poor</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Terrible</td>
<td>4</td>
</tr>
<tr>
<td>6 Extraintestinal manifestations</td>
<td>1 per manifestation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arthritis</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Uveitis</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Erythema nodosum</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Pyoderma gangenous</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Total Score (out of 19)*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*SCCAI ranges from 0 (best) to 19 (worst)
7.2.2 Total number of repeated measurements

The total number of entries for each questionnaire (SCCAI, IBD Control-8, CUCQ-8, EQ-5D, FCal, Hb, WCC, Plts, Alb, CRP, transferrin saturations, ferritin, endoscopy (UCEIS) histopathology (Nancy)), were counted on an entire cohort basis (see Chapter 2 for a full description of each repeated measurement). The median (IQR) number of responses were also calculated.

7.2.3 SCCAI

To interrogate the SCCAI, with the specific aim of evaluating the merit of including EIMs in the SCCAI, five approaches were taken. These were:

1. Examination of frequency of EIMs (Descriptor 6 of the SCCAI: arthritis, uveitis, erythema nodosum and pyoderma gangrenosum)
2. Correlation of the SCCAI descriptors (Descriptors 1 to 6)
3. Factor analysis of the SCCAI descriptors
4. Item-total correlation of the SCCAI descriptors
5. Cronbach’s alpha of the SCCAI descriptors

7.2.3.1 Frequency of reporting extraintestinal manifestations

To examine the contribution of EIMs, Descriptor 6 was expanded into its constituents: arthritis, uveitis, erythema nodosum and pyoderma gangrenosum. The frequency of each item (0 = not present and 1 = present) was calculated as an actual number and as a percentage of each patient’s total responses. Histograms for each EIM were constructed to display the distribution of responses in the entire pilot cohort.
7.2.3.2 Correlation between SCCAI descriptors

Correlation is a standard measure to quantify the extent to which two variables have a linear relationship with each other. Simple approaches towards measurement of correlation (for example Pearson or Spearman correlation) do not pose a problem if each observation is a single data point of paired measures (for example, correlating the height and weight of individuals drawn from a random sample), as there is no reason to expect that independence is not present. The assumption of independence is violated in repeated measures, in which each individual provides more than one data point. Repeated measurements correlation (rmcorr) overcomes the non-independence among observations by adjusting for inter-individual variability (248). Because rmcorr takes into account non-independence, it tends to yield much greater power than other techniques (249). For this reason, the R package ‘rmcorr’ was used for all correlation analyses in this chapter.

A correlation of +1 indicates a perfect positive association and -1 indicates a perfect negative association. The closer the correlation is to zero, the weaker the association. The following guide can be used to describe the strength of a correlation (250):

- 0.00 to 0.30 (0.00 to -0.30) negligible correlation
- 0.30 to 0.50 (-0.30 to -0.50) low positive (negative) correlation
- 0.50 to 0.70 (-0.50 to -0.70) moderate positive (negative) correlation
- 0.70 to 0.90 (-0.70 to -0.90) high positive (negative) correlation
- 0.90 to 1.00 (-0.90 to -1.00) very high positive (negative) correlation

A correlation table showing pair-wise correlation and 95% confidence intervals was constructed. Each descriptor in the table is correlated with each of the other descriptors, allowing visualisation of which pairs have the highest correlation. A cluster heat map was
then used to re-arrange the SCCAI descriptors corresponding to their similarity to each other. A cluster heat map is a hierarchically-clustered matrix coded to represent the magnitude of correlation. In this thesis, darker shades of red represent stronger negative and darker shades of blue stronger positive correlations.

7.2.3.3 Factor analysis of the SCCAI

To further examine the SCCAI, factor analysis was performed. Factor analysis is a statistical method used to describe variability among observed, correlated variables. The starting point of factor analysis is a correlation matrix (as in section 7.2.3.2 above). Groups of variables that have higher inter-correlations could well measure one underlying unobserved variable, which is called a latent factor. For example, it is possible that variations in six observed variables mainly reflect the variation in two latent factors. An essential step in factor analysis is to determine the appropriate number of factors. This was performed through parallel analysis which is a statistical method for determining the number of factors to retain.

As an exploratory step towards the latent structure of the SCCAI questionnaire, a first-order factor analysis was performed. All statistical computations were performed using R language, package ‘psych’ which was developed for assessment for of psychometric properties of rating scales and is used for the Personality Project (251). This package was designed primarily for multivariate analysis and scale construction using factor analysis, principal component analysis and cluster analysis.

Factor loadings are the correlation of the original variable to a latent factor. Communality for each variable are computed by taking the sum of the squared loadings for that variable.
The communality for a given variable can be interpreted as the proportion of variation in that
variable explained by the latent factors. For example, a communality of 0.45 would indicate
that 45% of the variation is explained by the factor model. Values close to one indicate that
the model explains most of the variation for that variable.

7.2.3.4 Item-total correlation of the SCCAI

Item-total correlation is used to determine if any of the descriptors within a questionnaire do
not have responses that vary in line with those for other descriptors. It is used to check if any
descriptor in a questionnaire is inconsistent with the averaged behavior of other descriptors.
A small item-total correlation provides evidence that the descriptor is not measuring the same
construct measured by the other descriptors included. A correlation value less than 0.3
indicates that the corresponding descriptor does not correlate very well with the index overall
and, thus, dropping this descriptor may be considered (252). The item-total correlation
analysis was performed using the R ‘rmcorr’ package. The correlation coefficients ($corr_i$)
between each of the constituent items $Item_i$ of the SCCAI scale ($i = 1$ to $6$) and the summary
SCCAI score without the correlated item:

$$corr_i = corr(Item_i, summary\ SCCAI - Item_i)$$

were computed.

7.2.3.5 Cronbach’s alpha and frequency analysis of the SCCAI

Cronbach’s alpha is a statistical measure to assess the internal consistency of a questionnaire
that comprises multiple descriptors and Likert-type scales. Internal consistency corresponds
to the extent to which it is a consistent measure of a construct, and the Cronbach’s alpha is
one way of measuring the strength of that consistency. The Cronbach’s alpha is computed by
correlating the score for each descriptor with the total score for each observation (in this case,
the total score for the SCCAI) and then comparing that to the variance for all individual descriptor scores:

\[ \alpha = \left( \frac{k}{k-1} \right) \left( 1 - \frac{\sum_{i=1}^{k} \sigma_i^2}{\sigma_T^2} \right) \]

where \( k \) is the number of descriptors within an index, \( \sigma_i^2 \) is the variance of a descriptor \( i \) and \( \sigma_T^2 \) corresponds to the variance associated with the total score. This was performed using the R package ‘psych’ and its function ‘alpha’. The resulting Cronbach’s alpha ranges from 0 to 1, providing an assessment of construct reliability. If all of items are completely independent from one another, then Cronbach’s alpha = 0; however, if all items are highly correlated then the Cronbach’s alpha approaches 1. The choice of ‘good’ values of a Cronbach’s alpha are arbitrary, however it is suggested that values should not be less than 0.7 (253).

Frequency analysis was also performed. The proportion of each sub-score for each descriptor was computed for the entire cohort. Each descriptor was assessed on the diversity of responses. For example, if all patients gave the same sub-score (i.e sub-score 0) for a certain descriptor (i.e., Descriptor 2), this would indicate that it does not discriminate between the levels of disease activity.
7.2.4 QoL indices

Similar to the methodology for the correlation for the SCCAI descriptors (rmcorr, section 7.2.3.2, page 161), correlation between the median SCCAI and QoL indices and between each of the QoL indices was performed. For each patient, the median SCCAI for the 2 weeks prior to each QoL entry was calculated. Missing values of SCCAI were omitted from the analysis (median (IQR) proportion missing SCCAI values = 0.145 (0.105, 0.155)). A correlation table showing pair-wise correlations between the median SCCAI and QoL indices was constructed.

A cluster heat map was then used to rearrange the median SCCAI and QoL indices corresponding to their level of correlation to each other. Cronbach’s alpha (see section 7.2.3.5, page 163), was performed for IBD Control-8 and CUCQ-8. This was based on the pair-wise correlation matrix which properly accounted for the repeated structure of the measurements.
7.2.5 Information loss

In this thesis, the concept of information loss means the information that would be lost if questionnaires were filled out at increased intervals. A critical response was defined as an SCCAI score of $\geq 5$. To test the hypothesis of whether the frequency of the SCCAI questionnaire had a significant impact on information loss, four experiments that simulated SCCAI prompts at different intervals: $k = 3$ days, $k = 5$ days, $k = 7$ days, $k = 14$ days, where $k$ is the interval between prompt messages, were performed.

Time stamps of responses were divided into a sequence of blocks, corresponding to each $k$ and responses were sampled uniformly at random from each block, simulating patients’ responses. A loss function ($\mathcal{L}$) was defined by the equation:

$$\mathcal{L} = 1 - \frac{\alpha}{\beta}$$

where, $\alpha$ is the total number of critical responses detected by the simulation model and $\beta$ is the number of intervals which contain at least one critical response (which is constant for each patient). After random sampling was repeated 1000 times, the median loss was calculated.
To explain the procedure, a 10 week period of one patient’s SCCAI responses was chosen. For this example, the simulation is for weekly prompts \( (k=7) \). Two (out of 1000) random simulated outcomes are displayed in Figure 7.1 (A) and (B). There are two intervals where SCCAI responses are \( \geq 5 \) (marked by \( \downarrow \)). The red dots are the responses that the simulation model has randomly chosen within the interval.

**Figure 7-1: Examples of simulated responses if prompts were sent weekly**

For the patient considered in the figures, the parameter \( \beta = 2 \) (the number of intervals with at least one critical response) while the parameter \( \alpha \) changes on each simulation run. In the example above, \( \alpha = 1 \) and \( \alpha = 0 \) for the first and the second random runs respectively as depicted in Figure 7-1 and the corresponding values of the loss function for each run are:

\[
\mathcal{L}_1 = 1 - \frac{1}{2} = 0.5 \quad \text{and} \quad \mathcal{L}_2 = 1 - \frac{0}{2} = 1
\]

which corresponds to 50% and 100% loss respectively.
7.2.6 Patterns of disease and clustering

Disease activity categories were defined by the total SCCAI score: remission (0,1,2), mild (3,4,5), moderate (6,7,8,9,10,11) and severe (≥12). For the 6 month pilot, the proportion of time each patient spent in each disease activity category was defined as:

\[ p_{ci}^j = \frac{n_{ci}^j}{n_{c1}^j + n_{c2}^j + n_{c3}^j + n_{c4}^j} \]

where \( p \) = proportion, \( j \) denotes a patient, \( c_i \) = disease category defined as: \( c_1 \) = remission, \( c_2 \) = mild, \( c_3 \) = moderate, \( c_4 \) = severe and \( n \) = number of SCCAI responses. A table was constructed that displayed each patient and the proportion of time spent in each disease activity category (as defined by \( p_{ci}^j \) above). Disease pattern is defined by a set of four \( p_{ci}^j \) values.

Principal component analysis (PCA) was then applied to the above data. PCA is a statistical procedure that converts sets of observations of possibly correlated variables into a set of values of linearly uncorrelated variables called principle components (PC). This transformation is defined in such a way that the first principal component has the largest possible variance, meaning that it accounts for as much of the variability in the data as possible. This is followed by the second largest variance and so on. For this analysis, principal component 1 (PC_1) and principal component 2 (PC_2) were plotted against each other to obtain a 2-dimensional plot. The percentage of variance explained by PC_1 and PC_2 was calculated.
Clustering was then performed. Clustering means to group a particular set of objects (in this case patients) based on their characteristics (in this case disease pattern), aggregating them according to their similarities. The clustering algorithm used was unsupervised, meaning that the computer algorithm determined the number of clusters. This was done through a technique known as affinity propagation, developed in 2007 (254). This technique works by randomly choosing a subset of representative examples to try to detect patterns in the data. These representative samples are known as exemplars. Similarities between pairs of data points are compared until a high-quality set of exemplars and corresponding clusters emerge.

It was important to consider the nature of the clinically relevant patient subgroups. Most studies investigating disease course in UC have been retrospective (255-258). A population-based cohort from Norway followed 519 patients with UC at 1, 5 and 10 years. Even though this was a prospective cohort, disease patterns were assessed by patients visualising four curves (indolent, worsening, relapsing and persistently active) and choosing which curve best described their disease course for the previous 5 or 10 years (259, 260).

After considering the studies and examining the TrueColours UC symptom graphs, three clinical categories were thought to cover most disease patterns seen in clinical practice in Oxford and in the TrueColours cohort over the 6 month pilot:

- remission (>80% time with SCCAI≤2, with no time spent with SCCAI≥5)
- relapsing pattern (some time spent in remission but with isolated episodes of SCCAI≥5 requiring an increase in medical therapy)
- persistently active (>80% time spent with SCCAI ≥3)
To determine whether clustering provided separation of different disease patterns, each patient, represented by a data point on the cluster plot, was thoroughly examined by AW, who had access to each patient’s medical file and full TrueColours UC data.

### 7.2.7 Flares

To explore algorithms that may assist in identifying exacerbation of disease activity, a flare was defined as SCCAI of $\geq 5$ for $\geq 3$ days and an increase of $\geq 1$. A rule based algorithm fitting the above criteria was constructed and applied to each patient's TrueColours UC disease course. A list of those patients with flares and the corresponding number of days spent in flare mode was tabulated. An example of how the flare detection algorithm worked is shown in Figure 7-2. All days that qualified as flare days are marked in vertical dotted red lines.

**Figure 7-2: An example of the flare detection algorithm superimposed on disease course**
7.2.8 **Faecal calprotectin (FCal)**

Correlations between FCal, SCCAI, UCEIS and Nancy index were computed using rmcorr (see section 7.2.3.2). To determine FCal distribution, both the UCEIS and Nancy values were separated into groups. There is currently no agreement on what defines remission and active disease for UCEIS and Nancy and so the groups were created using the following criteria.

For UCEIS, two scenarios were considered

- Remission = 0. Active disease ≥4.
  
  This resulted in three groups (Group 0: UCEIS 0, Group 1: UCEIS 1-3, Group 2: UCEIS 4-8)

- Remission ≤1. Active disease ≥4.
  
  This resulted in three groups (Group 0: UCEIS 0-1, Group 1: UCEIS 2-3, Group 2: UCEIS 4-8)

For Nancy, two scenarios were considered

- Remission = 0. Active disease ≥3.
  
  This resulted in three groups (Group 0: Nancy 0, Group 1: Nancy 1-2 and Group 2: Nancy 3-4)

- Remission ≤1. Active disease ≥2.
  
  This resulted in two groups (Group 0: Nancy 0-1 and Group 1: Nancy 2-4)

For combined UCEIS AND Nancy, two scenarios were considered

- Remission UCEIS 0 AND Nancy 0. Active disease UCEIS ≥4 AND Nancy ≥3.

- Remission UCEIS ≤1 AND Nancy ≤1. Active disease UCEIS ≥4 AND Nancy ≥3
The non-parametric Mann-Whitney $U$ test was applied to values of FCal to estimate statistical significance of their distribution in the above groups of each of the UCEIS, Nancy and combined criteria. Multinomial logistic regression was then used to predict the probability of group association based on the value of FCal. Contingency tables comparing predicted vs true values were then constructed.

The below equation for the classification function which was used to determine these cut-offs.

Classifier based on logistic function:

$$P(x) = \frac{1}{1 + \exp(-(a+b \cdot x))}$$

Threshold:

$$FCal_{\text{thresh}} = -\frac{1}{b} \left[ a + \ln\left(\frac{1 - k}{k}\right) \right]$$

where $P(x)$ is the classifier based on the logistic function. Using the area under the ROC curve, the best operating point of the logistic classifier was determined and the corresponding threshold was computed using the expression derived from above, with $FCal_{\text{thresh}}$ being the cut-off value and the $k$ is a threshold, where $a =$ intercept, $b =$ coefficient of the linear term.
7.2.9 *Blood results*

One of the experimental objectives of this research work was to understand whether the results of routine blood samples meaningfully describe the activity of UC. Patients were classified as remission or active disease, defined by a combination of UCEIS and the Nancy index. For this analysis, remission was defined as $UCEIS = 0 \text{ AND } Nancy = 0$. Active disease was defined as $UCEIS \geq 4 \text{ AND } Nancy \geq 3$. All episodes that did not fit either of these criteria were excluded from the analysis. The blood tests investigated in each group (remission vs active disease) were Hb, WCC, Plts, CRP, Alb within 2 weeks of endoscopy. For comparison, median SCCAI over the 2 weeks prior to and including the date of the endoscopy was also included in the analysis.

If patients did not have any variables within the above time frames, they were excluded from the analysis. This resulted in multiple initial sigmoidoscopies being excluded. Transferrin saturations, ferritin and FCal were also excluded from the analysis because there were multiple missing values within the defined proximity to the endoscopic procedure.

The data matrix comprised 6 variables and a column that classified the instances as either remission or active disease. The Mann-Whitney $U$ test was used to evaluate whether the above variables in one sample (eg active disease) tended to be larger than variables in the other (eg remission).

Histograms displaying each variable’s frequency in remission and active disease categories were constructed.
7.3 Results

The total number of measurements and median (IQR) entries per patient are displayed in Table 7-2.

Table 7-2: Total and median number of repeated measurements obtained in the 6 month TrueColours pilot

<table>
<thead>
<tr>
<th></th>
<th>Total number of measurements across entire pilot cohort</th>
<th>Median (IQR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCAI</td>
<td>8741</td>
<td>151 (102, 180)</td>
</tr>
<tr>
<td>IBD Control-8</td>
<td>827</td>
<td>14 (13,14)</td>
</tr>
<tr>
<td>CUCQ-8</td>
<td>827</td>
<td>14 (13,14)</td>
</tr>
<tr>
<td>EQ-5D</td>
<td>827</td>
<td>14 (13,14)</td>
</tr>
<tr>
<td>FCal</td>
<td>200</td>
<td>4 (3,6)</td>
</tr>
<tr>
<td>Hb</td>
<td>345</td>
<td>5 (3,7)</td>
</tr>
<tr>
<td>WCC</td>
<td>345</td>
<td>5 (3,7)</td>
</tr>
<tr>
<td>Plts</td>
<td>345</td>
<td>5 (3,7)</td>
</tr>
<tr>
<td>Alb</td>
<td>343</td>
<td>5 (3,7)</td>
</tr>
<tr>
<td>CRP</td>
<td>338</td>
<td>5 (3,7)</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>269</td>
<td>4 (3,6)</td>
</tr>
<tr>
<td>Ferritin</td>
<td>265</td>
<td>4 (3,5)</td>
</tr>
<tr>
<td>UCEIS</td>
<td>121</td>
<td>2 (2,2)</td>
</tr>
<tr>
<td>Nancy</td>
<td>120</td>
<td>2 (2,2)</td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical colitis Activity Index, CUCQ-8 = Crohn’s ulcerative colitis questionnaire-8, EQ-5D = generic quality of life scale, FCal = IBDoc™ faecal calprotectin, Hb = Haemoglobin, WCC = white cell count, Plts = platelets, Alb = albumin, CRP = C-reactive protein, UCEIS = ulcerative colitis endoscopic index of severity, Nancy = Nancy histopathological index
7.3.1  *SCCAI*

7.3.1.1  Frequency of reporting extraintestinal manifestations

The summary of usage of each of the EIMs is presented in Table 7-3. Almost half of the patients reported arthritis for an average of almost 50% of the time. Pyoderma gangrenosum was used by only one patient for 34% of the time, however, it was subsequently discovered that this patient was misusing the question as a way of recording his mouth ulcers. It illustrates the limitations of asking patients to record their own EIMs.

<table>
<thead>
<tr>
<th>Number of patients reporting extraintestinal manifestations</th>
<th>arthritis</th>
<th>uveitis</th>
<th>erythema nodosum</th>
<th>pyoderma gangrenosum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients reporting extraintestinal manifestations</td>
<td>31</td>
<td>9</td>
<td>5</td>
<td>1*</td>
</tr>
<tr>
<td>Average percentage of each patient’s total SCCAI entries</td>
<td>49.3%</td>
<td>25.9%</td>
<td>1.4%</td>
<td>33.6%*</td>
</tr>
</tbody>
</table>

*these results do not correspond to the actual meaning of the descriptor

Histograms displaying the number and frequency of each of the EIMs in this pilot cohort are displayed in Figure 7-3.
# 7.3.1.2 Correlation between SCCAI descriptors

Table 7-4 displays the pair-wise correlations between the SCCAI descriptors.

## Table 7-4: Pair-wise correlations between the SCCAI descriptors

<table>
<thead>
<tr>
<th>Descriptor 1 (q1)</th>
<th>Descriptor 2 (q2)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 2 (q2)</td>
<td>0.23</td>
<td>0.21 to 0.25</td>
</tr>
<tr>
<td>Descriptor 3 (q3)</td>
<td>0.38</td>
<td>0.37 to 0.40</td>
</tr>
<tr>
<td>Descriptor 4 (q4)</td>
<td>0.37</td>
<td>0.35 to 0.39</td>
</tr>
<tr>
<td>Descriptor 5 (q5)</td>
<td>0.31</td>
<td>0.30 to 0.33</td>
</tr>
<tr>
<td>Descriptor 6 (q6)</td>
<td>0.07</td>
<td>0.05 to 0.09</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Descriptor 2 (q2)</th>
<th>Descriptor 3 (q3)</th>
<th>0.20</th>
<th>0.19 to 0.23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 4 (q4)</td>
<td>0.15</td>
<td>0.13 to 0.17</td>
<td></td>
</tr>
<tr>
<td>Descriptor 5 (q5)</td>
<td>0.24</td>
<td>0.22 to 0.26</td>
<td></td>
</tr>
<tr>
<td>Descriptor 6 (q6)</td>
<td>0.04</td>
<td>0.02, to 0.06</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Descriptor 3 (q3)</th>
<th>Descriptor 4 (q4)</th>
<th>0.39</th>
<th>0.38 to 0.41</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 5 (q5)</td>
<td>0.32</td>
<td>0.30 to 0.34</td>
<td></td>
</tr>
<tr>
<td>Descriptor 6 (q6)</td>
<td>0.12</td>
<td>0.10 to 0.15</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Descriptor 4 (q4)</th>
<th>Descriptor 5 (q5)</th>
<th>0.30</th>
<th>0.28 to 0.32</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 6 (q6)</td>
<td>0.07</td>
<td>0.05 to 0.09</td>
<td></td>
</tr>
</tbody>
</table>

| Descriptor 5 (q5) | Descriptor 6 (q6) | 0.15             | 0.133 to 0.174 |

Descriptor 1 (q1) = bowel frequency (day), Descriptor 2 (q2) = bowel frequency (night), Descriptor 3 (q3) = urgency of defaecation, Descriptor 4 (q4) = blood in stool, Descriptor 5 (q5) = general well-being, Descriptor 6 (q6) = extraintestinal manifestations
The cluster heat map below (Figure 7-4) rearranges the SCCAI descriptors corresponding to their similarity to each other. All descriptors are positively correlated and therefore coloured blue. The descriptor with the least correlation to other descriptors is Descriptor 6 (q6): extraintestinal manifestations. The vertical lines are called 'dendrograms' (tree-graphs) and they display the 'clusters' based on similarity.

Figure 7-4: Cluster heat map - pair-wise correlation between SCCAI descriptors

q1 = Descriptor 1 bowel frequency (day), q2 = Descriptor 2 bowel frequency (nocturnal), q3 = Descriptor 3 urgency of defaecation, q4 = Descriptor 4 blood in stool, q5 = Descriptor 5 general well-being, q6 = Descriptor 6 extraintestinal manifestations
7.3.1.3 Factor analysis of the SCCAI

The final number of SCCAI questionnaires examined was 8741. Each SCCAI had sub-scores for each of the six descriptors. Based on the parallel analysis, as presented in Figure 7-5, the suggested number of factors was 3 and the number of principal components was 2.

Figure 7-5: Parallel analysis for SCCAI

The output of the first-order latent factor analysis is presented in Table 7-5.

Table 7-5: Factor analysis for the SCCAI

<table>
<thead>
<tr>
<th>Descriptors of the SCCAI</th>
<th>Factor 1 (F1)</th>
<th>Factor 2 (F2)</th>
<th>Factor 3 (F3)</th>
<th>Communality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 1 (q1)</td>
<td>0.58</td>
<td>0.01</td>
<td>0.19</td>
<td>0.37</td>
</tr>
<tr>
<td>Descriptor 2 (q2)</td>
<td>0.19</td>
<td>0.01</td>
<td>0.66</td>
<td>0.47</td>
</tr>
<tr>
<td>Descriptor 3 (q3)</td>
<td>0.61</td>
<td>0.07</td>
<td>0.14</td>
<td>0.40</td>
</tr>
<tr>
<td>Descriptor 4 (q4)</td>
<td>0.63</td>
<td>0.02</td>
<td>0.05</td>
<td>0.39</td>
</tr>
<tr>
<td>Descriptor 5 (q5)</td>
<td>0.46</td>
<td>0.11</td>
<td>0.24</td>
<td>0.28</td>
</tr>
<tr>
<td>Descriptor 6 (q6)</td>
<td>0.09</td>
<td>0.99</td>
<td>0.02</td>
<td>1.00</td>
</tr>
<tr>
<td>Proportion variance</td>
<td>0.23</td>
<td>0.17</td>
<td>0.09</td>
<td></td>
</tr>
</tbody>
</table>

Descriptor 1 (q1) = bowel frequency (day), Descriptor 2 (q2) = bowel frequency (night), Descriptor 3 (q3) = urgency of defaecation, Descriptor 4 (q4) = blood in stool, Descriptor 5 (q5) = general well-being, Descriptor 6 (q6) = extraintestinal manifestations
The analysis yielded three latent factors explaining 49% of the variance for the entire six descriptors.

- Factor 1 included Descriptors 1,3,4 and 5. This explained 23% of the variance.
- Factor 2 included Descriptor 6. This explained 17% of the variance.
- Factor 3 included Descriptor 2. This explained 9% of the variance.

The latent structure with three factors as described in Table 7-5 is presented in Figure 7-6.

**Figure 7-6: Latent structure of the SCCAI factor analysis with three factors**

$q_1 = \text{Descriptor 1 bowel frequency (day)}, q_2 = \text{Descriptor 2 bowel frequency (nocturnal)}, q_3 = \text{Descriptor 3 urgency of defaecation}, q_4 = \text{Descriptor 4 blood in stool}, q_5 = \text{Descriptor 5 general well-being}, q_6 = \text{Descriptor 6 extraintestinal manifestations}, F_1 = \text{latent factor 1}, F_2 = \text{latent factor 2}, F_3 = \text{latent factor 3}$
7.3.1.4 **Item-total correlation of the SCCAI**

The resulting item-total correlation as presented in Table 7-6, indicates that the removal of Descriptor 6 (extraintestinal manifestations) (item-total correlation 0.143) and Descriptor 2 (nocturnal bowel frequency) (item-total correlation 0.284) could be considered. This is because an item-total correlation value of <0.3 means that the corresponding descriptor does not correlate well with the rest of the index.

<table>
<thead>
<tr>
<th>Descriptors of SCCAI</th>
<th>Item-total correlation</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 1</td>
<td>0.477</td>
<td>0.460 to 0.493</td>
</tr>
<tr>
<td>Descriptor 2</td>
<td>0.284*</td>
<td>0.264 to 0.303</td>
</tr>
<tr>
<td>Descriptor 3</td>
<td>0.497</td>
<td>0.481 to 0.513</td>
</tr>
<tr>
<td>Descriptor 4</td>
<td>0.453</td>
<td>0.437 to 0.470</td>
</tr>
<tr>
<td>Descriptor 5</td>
<td>0.441</td>
<td>0.423 to 0.457</td>
</tr>
<tr>
<td>Descriptor 6</td>
<td>0.143*</td>
<td>0.121 to 0.163</td>
</tr>
</tbody>
</table>

95% CI = 95% confidence interval, Descriptor 1 = bowel frequency (day), Descriptor 2 = bowel frequency (night), Descriptor 3 = urgency to defaecation, Descriptor 4 = blood in stool, Descriptor 5 = general well-being, Descriptor 6 = extraintestinal manifestations

*A correlation value less than 0.3 indicates that the corresponding item does not correlate very well with the scale overall and, thus, it may be dropped.

7.3.1.5 **Cronbach’s alpha and frequency analysis of the SCCAI**

Analysis showed that the SCCAI questionnaire (all six descriptors) was below the minimal acceptable reliability of 0.7, with a Cronbach’s alpha of 0.66 (95% CI 0.65, 0.67). Table 7-7 shows that most descriptors (Descriptors 1-5) appeared to be worthy of retention, resulting in a decrease in the Cronbach’s alpha if deleted. The one exception to this was Descriptor 6 (extraintestinal manifestations), which when deleted increased the Cronbach’s alpha to 0.68. As such, removal of this item could be considered.
Table 7-7: Cronbach’s alpha of the SCCAI index if descriptors are dropped

<table>
<thead>
<tr>
<th>SCCAI descriptor</th>
<th>Cronbach’s alpha</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 1</td>
<td>0.584</td>
<td>0.571 to 0.597</td>
</tr>
<tr>
<td>Descriptor 2</td>
<td>0.655</td>
<td>0.644 to 0.768</td>
</tr>
<tr>
<td>Descriptor 3</td>
<td>0.575</td>
<td>0.562 to 0.588</td>
</tr>
<tr>
<td>Descriptor 4</td>
<td>0.638</td>
<td>0.627 to 0.649</td>
</tr>
<tr>
<td>Descriptor 5</td>
<td>0.568</td>
<td>0.554 to 0.582</td>
</tr>
<tr>
<td>Descriptor 6</td>
<td>0.681</td>
<td>0.671 to 0.736</td>
</tr>
</tbody>
</table>

Descriptor 1 = bowel frequency (day), Descriptor 2 = bowel frequency (night), Descriptor 3 = urgency to defaecation, Descriptor 4 = blood in stool, Descriptor 5 = general well-being, Descriptor 6 = extraintestinal manifestations, 95% CI = 95% confidence interval

Frequency analysis, as presented in Table 7-8, demonstrates the proportion of sub-scores for each descriptor. For example, for Descriptor 1, patients gave sub-score ‘0’ in 75%, sub-score ‘1’ in 22%, sub-score ‘2’ in 3%, and sub-score ‘3’ in 0%.

Table 7-8: Frequency analysis (in proportion) for each descriptor

<table>
<thead>
<tr>
<th>SCCAI descriptor</th>
<th>Sub-score 0</th>
<th>Sub-score 1</th>
<th>Sub-score 2</th>
<th>Sub-score 3</th>
<th>Sub-score 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 1</td>
<td>0.75</td>
<td>0.22</td>
<td>0.03</td>
<td>0.00</td>
<td>NA</td>
</tr>
<tr>
<td>Descriptor 2</td>
<td>0.92</td>
<td>0.08</td>
<td>0.00</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Descriptor 3</td>
<td>0.51</td>
<td>0.42</td>
<td>0.06</td>
<td>0.00</td>
<td>NA</td>
</tr>
<tr>
<td>Descriptor 4</td>
<td>0.76</td>
<td>0.17</td>
<td>0.05</td>
<td>0.02</td>
<td>NA</td>
</tr>
<tr>
<td>Descriptor 5</td>
<td>0.47</td>
<td>0.44</td>
<td>0.08</td>
<td>0.01</td>
<td>0.00</td>
</tr>
<tr>
<td>Descriptor 6</td>
<td>0.76</td>
<td>0.21</td>
<td>0.03</td>
<td>0.00</td>
<td>0.00</td>
</tr>
</tbody>
</table>

Descriptor 1 = bowel frequency (day), Descriptor 2 = bowel frequency (night), Descriptor 3 = urgency to defaecation, Descriptor 4 = blood in stool, Descriptor 5 = general well-being, Descriptor 6 = extraintestinal manifestations, Sub-score = likert-like scale for each descriptor, NA means the descriptor did not have this number of sub-score
7.3.2 QoL indices

7.3.2.1 Correlation

Table 7-9 displays the pair-wise correlations between the median SCCAI and QoL indices and pair-wise correlations between the different QoL indices used in TrueColours UC.

Table 7-9: Pair-wise correlations between the median SCCAI and QoL indices

<table>
<thead>
<tr>
<th></th>
<th>Median SCCAI</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBD Control-8</td>
<td>-0.70</td>
<td>-0.74 to -0.66</td>
</tr>
<tr>
<td>CUCQ-8</td>
<td>0.76</td>
<td>0.72 to 0.79</td>
</tr>
<tr>
<td>EQ-VAS</td>
<td>-0.53</td>
<td>-0.58 to -0.47</td>
</tr>
<tr>
<td>TTO</td>
<td>-0.51</td>
<td>-0.57 to -0.45</td>
</tr>
<tr>
<td>**IBD Control-8</td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>CUCQ-8</td>
<td>-0.78</td>
<td>-0.81 to -0.75</td>
</tr>
<tr>
<td>EQ-VAS</td>
<td>0.61</td>
<td>0.56 to 0.66</td>
</tr>
<tr>
<td>TTO</td>
<td>0.57</td>
<td>0.51 to 0.62</td>
</tr>
<tr>
<td><strong>CUCQ-8</strong></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>EQ-VAS</td>
<td>-0.63</td>
<td>-0.61 to -0.58</td>
</tr>
<tr>
<td>TTO</td>
<td>-0.64</td>
<td>-0.68 to -0.59</td>
</tr>
<tr>
<td><strong>EQ-VAS</strong></td>
<td>**</td>
<td></td>
</tr>
<tr>
<td>TTO</td>
<td>0.48</td>
<td>0.42 to 0.54</td>
</tr>
</tbody>
</table>

CUCQ-8 = Crohn’s Ulcerative Colitis Questionnaire-8, EQ-VAS = EQ-5D Visual Analogue Scale, TTO = EQ-5D Time Trade Off, 95% CI = 95% confidence interval
The cluster heat map (Figure 7-7) rearranges the items according to their similarity with each other. Mutual positive correlation is coloured in blue, while negative correlation is coloured in red. It is immediately apparent that the median SCCAI positively correlates with CUCQ-8 and negatively correlates with all other indices. The vertical lines are called 'dendrograms' (tree-graphs), which display the 'clusters' based on similarity. Using the cut-offs listed (section 7.2.3.2, page 161), there was high correlation between the median SCCAI and both the IBD Control-8 (rmcorr = -0.7) and CUCQ-8 (rmcorr = 0.76), however only moderate correlation with the EQ-5D TTO (rmcorr = -0.51) and EQ-VAS (rmcorr = -0.53). Correlation between IBD-Control-8 and CUCQ-8 was high (-0.78). Both disease-specific QoL indices had correlation with EQ-5D TTO and EQ-VAS (IBD Control-8 0.57 and 0.61 and CUCQ-8 -0.64 and -0.63 respectively).

**Figure 7-7: Cluster heat map - pair-wise correlation between median SCCAI and QoL indices**

SCCAI = Simple Clinical Colitis Activity Index, IBD Control-8 = 8 question version of IBD Control, CUCQ-8 = Crohn’s Ulcerative Colitis Questionnaire – 8 questions. TTO = ED-5D time trade off, EQ-VAS = ED-5D visual analogue scale
7.3.2.2 Cronbach’s alpha of the QoL indices

Analysis of the IBD Control-8 and the CUCQ-8 showed Cronbach’s alpha values of 0.77 (95% CI 0.690-0.860) and 0.85 (95% CI 0.790-0.900) respectively (Table 7-10 and Table 7-11). All descriptors for both indices are worthy of retention, all resulting in a decrease in the Cronbach’s alpha if deleted.

Table 7-10: Cronbach’s alpha of IBD Control-8 if descriptors are dropped

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Cronbach’s alpha</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 1</td>
<td>0.73</td>
<td>0.622 to 0.838</td>
</tr>
<tr>
<td>Descriptor 2</td>
<td>0.75</td>
<td>0.650 to 0.850</td>
</tr>
<tr>
<td>Descriptor 3</td>
<td>0.74</td>
<td>0.638 to 0.842</td>
</tr>
<tr>
<td>Descriptor 4</td>
<td>0.75</td>
<td>0.650 to 0.850</td>
</tr>
<tr>
<td>Descriptor 5</td>
<td>0.74</td>
<td>0.637 to 0.846</td>
</tr>
<tr>
<td>Descriptor 6</td>
<td>0.76</td>
<td>0.664 to 0.856</td>
</tr>
<tr>
<td>Descriptor 7</td>
<td>0.75</td>
<td>0.650 to 0.850</td>
</tr>
<tr>
<td>Descriptor 8</td>
<td>0.77</td>
<td>0.680 to 0.860</td>
</tr>
</tbody>
</table>

Descriptor 1 = Your IBD has been well controlled in the past 2 weeks, Descriptor 2 = Your current treatment is useful in controlling your IBD, Descriptor 3 = In the past 2 weeks, did you miss any of your planned activities due to your IBD? Descriptor 4 = In the past 2 weeks did you wake up at night because of your symptoms of IBD? Descriptor 5 = In the past 2 weeks did you suffer any significant pain or discomfort? Descriptor 6 = In the past 2 weeks did you often feel lacking in energy (fatigue)? Descriptor 7 = In the last 2 weeks did you feel anxious or depressed due to your IBD? Descriptor 8 = In the past 2 weeks did you think that you needed a change in treatment?

Table 7-11: Cronbach’s alpha of CUCQ-8 if descriptors are dropped

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Cronbach’s alpha</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Descriptor 1</td>
<td>0.82</td>
<td>0.750 to 0.920</td>
</tr>
<tr>
<td>Descriptor 2</td>
<td>0.82</td>
<td>0.750 to 0.920</td>
</tr>
<tr>
<td>Descriptor 3</td>
<td>0.82</td>
<td>0.748 to 0.892</td>
</tr>
<tr>
<td>Descriptor 4</td>
<td>0.82</td>
<td>0.750 to 0.920</td>
</tr>
<tr>
<td>Descriptor 5</td>
<td>0.83</td>
<td>0.762 to 0.898</td>
</tr>
<tr>
<td>Descriptor 6</td>
<td>0.83</td>
<td>0.764 to 0.896</td>
</tr>
<tr>
<td>Descriptor 7</td>
<td>0.85</td>
<td>0.790 to 0.910</td>
</tr>
<tr>
<td>Descriptor 8</td>
<td>0.83</td>
<td>0.762 to 0.898</td>
</tr>
</tbody>
</table>

Descriptor 1 = On how many days over the last 2 weeks have you felt tired? Descriptor 2 = In the last 2 weeks did your bowel condition prevent you from going out socially? Descriptor 3 = On how many days over the past 2 weeks have you felt generally unwell? Descriptor 4 = On how many days over the last 2 weeks have you felt pain in your abdomen? Descriptor 5 = On how many nights in the last 2 weeks have you had to get up to use the toilet because of your bowel condition after you have gone to bed? Descriptor 6 = On how many days over the last 2 weeks has your abdomen felt bloated? Descriptor 7 = In the last 2 weeks have you felt upset? Descriptor 8 = On how many days over the last two weeks have you had to rush to the toilet?
7.3.3 Information loss

45/59 patients had at least one critical response (defined as an SCCAI ≥5) within the 6 month pilot. The median loss in each of the intervals \(k\) for each patient is summarised in Table 7-12. For a full statistical summary of the simulated response at different intervals, please see Appendix N.

Table 7-12: Proportion of critical points (SCCAI ≥5) lost with lengthening intervals

<table>
<thead>
<tr>
<th>Patient</th>
<th>(k =3^*)</th>
<th>(k =5^*)</th>
<th>(k =7^*)</th>
<th>(k =14^*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.556</td>
<td>0.667</td>
<td>0.75</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>1.000</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>0.556</td>
<td>0.625</td>
<td>0.714</td>
<td>0.75</td>
</tr>
<tr>
<td>4</td>
<td>0.400</td>
<td>0.583</td>
<td>0.636</td>
<td>0.714</td>
</tr>
<tr>
<td>5</td>
<td>0.600</td>
<td>0.75</td>
<td>0.667</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>0.444</td>
<td>0.652</td>
<td>0.714</td>
<td>0.769</td>
</tr>
<tr>
<td>7</td>
<td>0.500</td>
<td>0.6</td>
<td>0.636</td>
<td>0.6</td>
</tr>
<tr>
<td>8</td>
<td>0.143</td>
<td>0.222</td>
<td>0.167</td>
<td>0.333</td>
</tr>
<tr>
<td>9</td>
<td>0.538</td>
<td>0.6</td>
<td>0.75</td>
<td>0.8</td>
</tr>
<tr>
<td>10</td>
<td>0.417</td>
<td>0.6</td>
<td>0.667</td>
<td>0.833</td>
</tr>
<tr>
<td>11</td>
<td>0.267</td>
<td>0.478</td>
<td>0.471</td>
<td>0.6</td>
</tr>
<tr>
<td>12</td>
<td>0.000</td>
<td>0.5</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>0.500</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>14</td>
<td>0.250</td>
<td>0.25</td>
<td>0.333</td>
<td>0.4</td>
</tr>
<tr>
<td>15</td>
<td>0.636</td>
<td>0.8</td>
<td>0.778</td>
<td>0.833</td>
</tr>
<tr>
<td>16</td>
<td>1.000</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>17</td>
<td>0.500</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>0.545</td>
<td>0.727</td>
<td>0.8</td>
<td>0.875</td>
</tr>
<tr>
<td>19</td>
<td>0.500</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>0.667</td>
<td>0.667</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>0.429</td>
<td>0.6</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>22</td>
<td>0.750</td>
<td>0.75</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>23</td>
<td>0.471</td>
<td>0.583</td>
<td>0.7</td>
<td>0.714</td>
</tr>
<tr>
<td>24</td>
<td>0.462</td>
<td>0.6</td>
<td>0.571</td>
<td>0.7</td>
</tr>
<tr>
<td>25</td>
<td>0.444</td>
<td>0.577</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>26</td>
<td>0.200</td>
<td>0.333</td>
<td>0.333</td>
<td>0.375</td>
</tr>
<tr>
<td>27</td>
<td>0.500</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>28</td>
<td>0.412</td>
<td>0.625</td>
<td>0.667</td>
<td>0.75</td>
</tr>
<tr>
<td>29</td>
<td>0.100</td>
<td>0.158</td>
<td>0.143</td>
<td>0.25</td>
</tr>
<tr>
<td>30</td>
<td>0.118</td>
<td>0.25</td>
<td>0.333</td>
<td>0.5</td>
</tr>
<tr>
<td>31</td>
<td>0.667</td>
<td>0.833</td>
<td>0.833</td>
<td>1</td>
</tr>
<tr>
<td>32</td>
<td>0.375</td>
<td>0.417</td>
<td>0.444</td>
<td>0.462</td>
</tr>
<tr>
<td>33</td>
<td>0.571</td>
<td>0.636</td>
<td>0.7</td>
<td>0.875</td>
</tr>
<tr>
<td></td>
<td>Median loss (IQR)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>-----------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>0.500 (0.412,0.571)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>0.600 (0.5,0.75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>0.667 (0.5,0.833)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>0.800 (0.6,1.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SCCAI = Simple Clinical Colitis Activity Index, \( k \) = simulated interval between prompt messages being sent, *information missed is compared to baseline daily SCCAI entry, IQR = interquartile range

Histograms to display the distribution of loss for each interval are shown in Figure 7-8 below.

**Figure 7-8: Distribution of loss for each simulated interval**

\( k = \) simulated interval (in days) between prompt messages being sent
7.3.4 Patterns of disease and clustering

The proportion of time each patient spent in each SCCAI disease activity category ($p_{ci}$) is shown in Table 7-13.

Table 7-13: Proportion of time spent in each SCCAI activity category

<table>
<thead>
<tr>
<th>Patient</th>
<th>Remission</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.038</td>
<td>0.929</td>
<td>0.033</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0.84</td>
<td>0.16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0.678</td>
<td>0.288</td>
<td>0.034</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>0.317</td>
<td>0.639</td>
<td>0.044</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>0.951</td>
<td>0.049</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0.984</td>
<td>0.016</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0.96</td>
<td>0.04</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>0.325</td>
<td>0.675</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>0.076</td>
<td>0.817</td>
<td>0.107</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>0.465</td>
<td>0.293</td>
<td>0.242</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>0.876</td>
<td>0.124</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>12</td>
<td>0.634</td>
<td>0.127</td>
<td>0.211</td>
<td>0.028</td>
</tr>
<tr>
<td>13</td>
<td>0.613</td>
<td>0.376</td>
<td>0.012</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>0.377</td>
<td>0.448</td>
<td>0.175</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>0.856</td>
<td>0.122</td>
<td>0.022</td>
<td>0</td>
</tr>
<tr>
<td>16</td>
<td>0.918</td>
<td>0.054</td>
<td>0.027</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>0.422</td>
<td>0.22</td>
<td>0.349</td>
<td>0.009</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>0.855</td>
<td>0.129</td>
<td>0.016</td>
</tr>
<tr>
<td>19</td>
<td>0.891</td>
<td>0.109</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>20</td>
<td>0.89</td>
<td>0.11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>21</td>
<td>0.782</td>
<td>0.218</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>22</td>
<td>0.238</td>
<td>0.743</td>
<td>0.02</td>
<td>0</td>
</tr>
<tr>
<td>23</td>
<td>0.991</td>
<td>0.009</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24</td>
<td>0.962</td>
<td>0.025</td>
<td>0.012</td>
<td>0</td>
</tr>
<tr>
<td>25</td>
<td>0.994</td>
<td>0.006</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>26</td>
<td>0.654</td>
<td>0.333</td>
<td>0.012</td>
<td>0</td>
</tr>
<tr>
<td>27</td>
<td>0.618</td>
<td>0.336</td>
<td>0.046</td>
<td>0</td>
</tr>
<tr>
<td>28</td>
<td>0.88</td>
<td>0.114</td>
<td>0.006</td>
<td>0</td>
</tr>
<tr>
<td>29</td>
<td>0.952</td>
<td>0.048</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>30</td>
<td>0.627</td>
<td>0.317</td>
<td>0.056</td>
<td>0</td>
</tr>
<tr>
<td>31</td>
<td>0.258</td>
<td>0.589</td>
<td>0.153</td>
<td>0</td>
</tr>
<tr>
<td>32</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>33</td>
<td>0.128</td>
<td>0.513</td>
<td>0.333</td>
<td>0.026</td>
</tr>
<tr>
<td>34</td>
<td>0.888</td>
<td>0.107</td>
<td>0.006</td>
<td>0</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
<td>0.965</td>
<td>0.035</td>
<td>0</td>
</tr>
<tr>
<td>36</td>
<td>0.487</td>
<td>0.18</td>
<td>0.333</td>
<td>0</td>
</tr>
<tr>
<td>37</td>
<td>0.587</td>
<td>0.238</td>
<td>0.174</td>
<td>0</td>
</tr>
<tr>
<td>38</td>
<td>0.8</td>
<td>0.169</td>
<td>0.031</td>
<td>0</td>
</tr>
<tr>
<td>39</td>
<td>0</td>
<td>0.859</td>
<td>0.141</td>
<td>0</td>
</tr>
<tr>
<td>40</td>
<td>0.311</td>
<td>0.623</td>
<td>0.066</td>
<td>0</td>
</tr>
</tbody>
</table>
Principal component analysis was performed using four principal components. The proportion of variance explained by each principal component is shown below in Table 7-14.

Principal component 1 accounted for 93.5% of the variance.

Table 7-14: Proportion of variance explained by each principal component

<table>
<thead>
<tr>
<th>Principal Components</th>
<th>Proportion of variance explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Principal Component 1</td>
<td>0.9350131</td>
</tr>
<tr>
<td>Principal Component 2</td>
<td>0.0648311</td>
</tr>
<tr>
<td>Principal Component 3</td>
<td>0.0001557</td>
</tr>
<tr>
<td>Principal Component 4</td>
<td>&lt;0.000001</td>
</tr>
</tbody>
</table>
Figure 7-9 displays the cluster plot. The unsupervised cluster plot resulted in 5 clusters being identified. For this analysis, these clusters have been labelled as A, B, C, D, E.

**Figure 7-9: TrueColours UC pilot cohort disease pattern cluster plot**

![Cluster Plot](image)

PC_1 = principal component 1, PC_2 = principal component 2

In Cluster A, 24/25 patients in this cluster were in remission for >80% of the 6 month pilot. However, 4/25 patients in this cluster also experienced an exacerbation as defined by a SCCAI≥8. A representative example of a patient in this cluster is shown as (1) in Figure 7-9 above. This patient’s disease pattern during the 6 month pilot was remission 92%, mild 5%, moderate 3% and severe 0% of the time.
The remaining clusters represented different patterns of active disease.

In Cluster B, 7/11 patients experienced an exacerbation with an SCCAI ≥8, requiring oral prednisolone therapy. The other 4/11 patients had milder exacerbations, but spent over 60% of time in remission. A representative example of a patient in this cluster is shown as (2) in Figure 7-9 above. This patient’s disease pattern during the 6 month pilot was remission 59%, mild activity 24%, moderate activity 17% and severe activity 0% of the time.

In Cluster C, all patients had some active disease, but the disease pattern was not as clear as in other groups. Combinations of remission, mild or moderately active disease varied sufficiently that they did not clearly fit into Clusters B, D or E. A representative example of a patient in this cluster is shown as (3) in Figure 7-9 above. This patient’s disease pattern over the 6 month pilot was remission 50%, mild activity 46%, moderate activity 4%, and severe activity 0% of the time.

In Group D, 3/3 patients spent >50% in mild disease activity and >30% in moderate disease activity. A representative example of a patient in this cluster is shown as (4) in Figure 7-9 above. This patient’s disease pattern over the 6 month pilot was remission 13%, mild activity 51%, moderate activity 33%, and severe activity 3% of the time.

In Group E, 6/6 patients spent <5% in remission and >80% in mild disease activity. A representative example of a patient in this cluster is shown as (5) in Figure 7-9 above. This patient’s disease pattern over the 6 month pilot was remission 4%, mild activity 93%, moderate activity 3%, and severe activity 0% of the time.
7.3.5 Flares

Using the flare algorithm, 30 patients qualified as having a flare. For these patients, the median (IQR) time spent in flare over the 6 month pilot was 13.5 (5.3, 34.8) days. Distribution of days spent in flare is displayed in Figure 7-10.

Figure 7-10: Flares identified using a flare algorithm in the TrueColours pilot

7.3.6 Faecal calprotectin (FCal)

Correlations between FCal and SCCAI, UCEIS and Nancy are presented in Table 7-15. There was low correlation between FCal and SCCAI but high correlation between FCal and both the UCEIS and Nancy index.

Table 7-15: Pair-wise correlations between FCal and other indices

<table>
<thead>
<tr>
<th></th>
<th>FCal</th>
<th>95%CI</th>
<th>Number of instances</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCCAI (median 5 days prior to FCal)</td>
<td>0.311</td>
<td>0.159 to 0.449</td>
<td>198</td>
<td>0.000148</td>
</tr>
<tr>
<td>UCEIS (within 14 days of FCal)</td>
<td>0.701</td>
<td>0.243 to 0.903</td>
<td>53</td>
<td>0.003617</td>
</tr>
<tr>
<td>Nancy (within 14 days of FCal)</td>
<td>0.829</td>
<td>0.511 to 0.947</td>
<td>53</td>
<td>0.000134</td>
</tr>
</tbody>
</table>

FCal = IBDoc® faecal calprotectin (measured in µg/g of faeces), 95% CI = 95 % confidence intervals, Number of instances relates to the number of times that a correlation could be made between Fcal and indices, SCCAI – median for 5 days prior to FCal, UCEIS within 14 days of FCal, Nancy within 14 days of FCal.
The distribution of the FCal values for the UCEIS groups are presented in Figure 7-11.

**Figure 7-11: Distribution of FCal by UCEIS groups**

![Distribution of FCal by UCEIS groups](image)

FCal = IBDoc® faecal calprotectin (measured in µg/g of faeces)
UCEIS = Ulcerative Colitis Endoscopic Index of Severity: scores range from 0 (best) to 8 (worst)

(A): UCEIS scores were divided into three groups (UCEIS 0, 1-3, and 4-8).
(B): UCEIS scores were divided into three groups (UCEIS 0-1, 2-3, and 4-8)

The statistical significance of FCal distribution between the UCEIS groups is presented in Table 7-16.

**Table 7-16: Statistical significance of FCal distribution between the UCEIS groups (p-values)**

<table>
<thead>
<tr>
<th>(A)</th>
<th>UCEIS</th>
<th>1-3</th>
<th>4-8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0.082206</td>
<td>0.000125</td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>0.000249</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(B)</th>
<th>UCEIS</th>
<th>2-3</th>
<th>4-8</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-1</td>
<td>0.018632</td>
<td>0.000012</td>
</tr>
<tr>
<td></td>
<td>2-3</td>
<td></td>
<td>0.027038</td>
</tr>
</tbody>
</table>

All results are presented as p-values. UCEIS = Ulcerative Colitis Endoscopic Index of Severity (scores range from 0 (best) to 8 (worst)).

(A): UCEIS scores were divided into three groups (UCEIS 0, 1-3, and 4-8).
(B): UCEIS scores were divided into three groups (UCEIS 0-1, 2-3, and 4-8)
Contingency tables for the UCEIS groups are presented in Figure 7-12.

**Figure 7-12: Contingency tables for predicted and true UCEIS groups**

(UCEIS = Ulcerative Colitis Endoscopic Index of Severity: scores range from 0 (best) to 8 (worst))

(A): UCEIS scores were separated into three groups (UCEIS 0, 1-3, and 4-8)

(B): UCEIS scores were separated into three groups (UCEIS 0-1, 2-3, 4-8)
The distribution of FCal values for the Nancy groups are presented in Figure 7-13.

**Figure 7-13: Distribution of FCal by Nancy groups**

(A) Nancy scores were divided into three groups (Nancy 0-1, 2-3, and 4-4)

(B) Nancy scores were divided into two groups (Nancy 0-1, and 2-4)

![Box plots for FCal distribution by Nancy groups](image)

Nancy = Nancy histopathological index: scores range from 0 (best) to 4 (worst)

(A): Nancy scores were divided into three groups (Nancy 0, 1-2, and 3-4)

(B): Nancy scores were divided into two groups (Nancy 0-1, and 2-4)

The statistical significance of FCal distribution between the Nancy groups is presented in Table 7-17.

**Table 7-17: Statistical significance of FCal distribution between Nancy groups (p-values)**

<table>
<thead>
<tr>
<th>(A)</th>
<th>Nancy</th>
<th>1-2</th>
<th>3-4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0.002843</td>
<td>0.00001</td>
</tr>
<tr>
<td></td>
<td>1-2</td>
<td>0.012264</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>(B)</th>
<th>Nancy</th>
<th>2-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>0.000009</td>
<td></td>
</tr>
</tbody>
</table>

All results are presented as p-values. Nancy = Nancy histopathological index: scores range from 0 (best) to 4 (worst)

(A): Nancy scores were divided into three groups (Nancy 0, 1-2, and 3-4)

(B): Nancy scores were divided into two groups (Nancy 0-1, and 2-4)
Contingency tables for Nancy groups are presented in Figure 7-14.

**Figure 7-14: Contingency tables for predicted and true Nancy groups**

Nancy = Nancy histopathological index: scores range from 0 (best) to 4 (worst)
A): Nancy scores were divided into three groups (Nancy 0,1-2, and 3-4)
(B): Nancy scores were divided into two groups (Nancy 0-1, and 2-4)
The distributions of FCal values for the combined UCEIS AND Nancy criteria for remission and active disease are presented in Figure 7-15.

**Figure 7-15: Distribution of FCal for remission and active disease**

(A) Remission defined as UCEIS = 0 AND Nancy = 0. Active disease defined as UCEIS ≥4 AND Nancy ≥3.

(B) Remission defined as UCEIS = 0 -1 AND Nancy <=1. Active disease defined as UCEIS ≥4 AND Nancy ≥2.

The statistical significance of FCal distribution between the combined UCES AND Nancy is presented in Table 7-18.

**Table 7-18: Statistical significance of FCal distribution for combined UCEIS AND Nancy criteria (p-values)**

<table>
<thead>
<tr>
<th></th>
<th>Remission UCEIS 0 AND Nancy 0</th>
<th>Active</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active disease UCEIS ≥4 AND Nancy ≥3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>0.000009</td>
<td></td>
</tr>
<tr>
<td>Remission</td>
<td>0.000001</td>
<td></td>
</tr>
</tbody>
</table>


Contingency tables for remission and active groups are presented in Figure 7-16.

**Figure 7-16: Contingency tables for predicted and true remission and active disease**

(A) Remission defined as UCEIS = 0 \text{ AND } \text{Nancy} = 0. Active disease defined as UCEIS ≥4 \text{ AND } \text{Nancy} ≥3.

(B) Remission defined as UCEIS = 0 -1 \text{ AND } \text{Nancy} ≤1. Active disease defined as UCEIS ≥4 \text{ AND } \text{Nancy} ≥2.

A summary of the classification procedure for remission and active disease for all defined UCEIS, Nancy and combined criteria options are shown in Table 7-19.

**Table 7-19: Summary of classification procedure for remission and active disease groups**

<table>
<thead>
<tr>
<th>Cut-off Fecal (µg/g)</th>
<th>418</th>
<th>338</th>
<th>260</th>
<th>324</th>
<th>147</th>
<th>180</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accuracy</td>
<td>80%</td>
<td>78%</td>
<td>82%</td>
<td>70%</td>
<td>86%</td>
<td>82%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td>78%</td>
<td>76%</td>
<td>78%</td>
<td>68%</td>
<td>85%</td>
<td>82%</td>
</tr>
<tr>
<td>Specificity</td>
<td>83%</td>
<td>80%</td>
<td>88%</td>
<td>71%</td>
<td>89%</td>
<td>82%</td>
</tr>
<tr>
<td>ROC AUC</td>
<td>0.903</td>
<td>0.894</td>
<td>0.917</td>
<td>0.752</td>
<td>0.888</td>
<td>0.920</td>
</tr>
</tbody>
</table>

Fecal = IBDoc \text{©} faecal calprotectin (measured in µg/g of faeces)
UCEIS = Ulcerative Colitis Endoscopic Index of Severity, Nancy = Nancy Histopathologic Index where
7.3.7 Blood results

For differentiation between remission and active disease, there were 48 events (in 25 unique patients) classified as either remission (n = 19) or active disease (n = 29). There were 71 events which did not fall into either of these categories and were excluded from the analysis. After removing instances with missing SCCAI or blood test results, there were 36 events for analysis (remission (14), active (22)). The data matrix therefore consisted of 36 events each with six variables.

Table 7-20 displays the ability of the different variables to distinguish between remission and active disease. Sample sizes are low, but a trend can be seen for median SCCAI, Plt, WCC and CRP. For full statistical data on each event of remission or active disease, please refer to Appendix O.

Table 7-20: Ability of different variables to distinguish between remission and active disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>p value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median SCCAI</td>
<td>0.0001</td>
</tr>
<tr>
<td>Hb</td>
<td>0.4188</td>
</tr>
<tr>
<td>WCC</td>
<td>0.0009</td>
</tr>
<tr>
<td>Plt</td>
<td>0.0132</td>
</tr>
<tr>
<td>Alb</td>
<td>0.0215</td>
</tr>
<tr>
<td>CRP</td>
<td>0.0084</td>
</tr>
</tbody>
</table>

*Mann-Whitney U test used to assess variables in each group (remission vs active disease) Remission defined as UCEIS = 0 AND Nancy Index = 0. Active disease is defined as UCEIS ≥4 AND Nancy index≥3.
Histograms displaying each variable’s frequency in remission and active disease categories are shown in Figure 7-17. Overlap between remission and active disease groups is represented in pink.

**Figure 7-17: Frequency of instances in remission and active disease for each variable**

SCCAI = Simple Clinical Colitis Activity Index, hb = haemoglobin, wcc = white cell count, crp = c-reactive protein, Remission defined as endoscopic UCEIS = 0 AND histopathologic Nancy index = 0

Active disease defined as endoscopic UCEIS ≥4 and histopathologic Nancy index ≥3
7.4 Discussion

The TrueColours UC pilot followed 66 patients for 6 months resulting in over 14,000 data entry points. Different approaches were used to analyse the longitudinal repeated measurements. Close examination of the SCCAI descriptors was possible. The three QoL indices collected by TrueColours (IBD Control-8, CUCQ-8 and EQ-5D) were correlated both with the median SCCAI for the preceding two weeks and with each other. The concept of information loss with increasing intervals of data collection was explored. A novel way to phenotype patients through disease pattern clustering was successful. A flare detection algorithm was also able to be superimposed upon patients’ disease courses. Strict endoscopic and histopathologic criteria for remission and active disease were used to explore faecal calprotectin cut-offs. These same objective measures were used to determine whether blood results or the SCCAI could distinguish between remission and active disease.

Data from this pilot indicate that EIMs should be removed from the SCCAI. EIMs need to be independently assessed, but not as part of disease activity assessment. All five analyses performed on the SCCAI (frequency of EIMs reported, correlation between the SCCAI descriptors, factor analysis, item-total correlation and reliability analysis) indicated that EIMs correlated poorly with other markers of disease activity in the SCCAI. Arthritis was the only EIM that was reported frequently. Correlation of EIMs as a group (using rmcorr) showed negligible correlation with any of the other descriptors. The factor analysis identified that one of the latent factors was EIMs alone. The item-total correlation and reliability analysis also suggested that removal of the EIM descriptor would improve overall disease activity assessment. This pilot also demonstrated that asking patients to report EIMs can be unreliable. None of the EIMs reported were formally validated. For example, it is unlikely that 31 patients had true inflammatory arthritis (that is they would not be considered to have...
an EIM if this descriptor had been answered by a physician). The example of the patient using pyoderma gangrenosum to report mouth ulceration highlights the unreliability of this method of reporting EIMs. For the above reasons, this work supports the removal of EIMs from the SCCAI. Reliability of reporting EIMs may be improved if physicians were asked to report EIMs however this would not be feasible through a programme such as TrueColours UC which relies on patients reporting their symptoms remotely.

Interestingly, nocturnal bowel frequency (Descriptor 2) was also identified as a weak component of the SCCAI. It was not as weak as EIMs, but correlation with other descriptors was poor (rmcorr 0.04 to 0.24) and factor analysis identified that one of the latent factors was nocturnal bowel frequency alone. Item-total correlation for this descriptor also fell below the suggested threshold of 0.3 for retention of items. Some of this may have been cohort dependent as frequency analysis revealed that 92% of responses did not report any nocturnal bowel movements. Although the removal of this descriptor during the reliability analysis did not increase the Cronbach’s alpha (as in the case of EIMs), it only led to a small decrease in the Cronbach’s alpha. A larger cohort would be needed to replicate these results prior to recommending the removal of nocturnal bowel frequency from the SCCAI.

In this pilot, the Cronbach’s alpha of the symptom-based SCCAI index did not meet the minimum acceptable value of 0.70 (Cronbach’s alpha of 0.66), whereas the IBD Control-8 and CUCQ-8 had Cronbach’s alpha values of 0.77 and 0.85 respectively. There are no previously published Cronbach’s alpha values for SCCAI however previously published Cronbach’s alpha values for IBD Control-8 and CUCQ-8 were 0.86 (111) and 0.88 (113) respectively, similar to the current data. The SCCAI was developed in 1998 before modern criteria for index development were developed. This is in contrast to the IBD Control and
CUCQ-8, both of which adhered to development and validation criteria, emphasising the value of following these criteria.

Correlation of repeated measurements between SCCAI with QoL indices was high for the IBD Control-8 (rmcorr = 0.70) and CUCQ-8 (rmcorr = 0.76). For IBD Control-8, this was similar to what was reported in the development and validation study for this index (111). For the CUCQ-8, the correlation was higher than previously reported (113). This supports the use of IBD disease-specific QoL PROMs because it indicates a high correlation with disease activity while also allowing other symptoms such as anxiety and fatigue to be collected and monitored. This is the first time that IBD Control-8 and CUCQ-8 have been correlated. This correlation was high, which is to be expected given that similar symptoms and consequences are covered. This indicates that there is no point for a system like TrueColours to collect both.

There was moderate correlation of both measures of the generic EQ-5D (TTO and EQ-VAS) and the median SCCAI (rmcorr -0.51 and -0.53 respectively). There was also moderate to high correlation between the EQ-5D and IBD-Control and CUCQ-8. Given this correlation, it appears worthwhile collecting this data through TrueColours UC because it enables comparisons with other chronic diseases and health economic analysis.

To assist in answering the question of how often to collect symptom data a simulation model was created to estimate the information loss that occurs with increasing intervals between prompts. The model assumes that adherence to questionnaires is 100% (even though mean adherence to daily questionnaires was 75%) so may underestimate loss. It also assumes that patients are equally likely to respond to the questionnaire in the interval allowed, regardless
of their symptoms on that particular day. Critical points were defined as an SCCAI $\geq 5$, because this level of disease was considered to be clinically relevant. If a higher threshold was used, less critical information would be lost. Compared to daily entry, a median 50% of critical points were lost when the interval was increased from one to three days and up to 80% when the interval was increased to every 14 days. There is a balance to be struck between daily questionnaires and user fatigue. To maximise capture of critical points, algorithms for modulating frequency of questionnaires based on recent disease pattern need to be considered.

Clustering patients by their disease pattern may prove useful. A weakness of this approach is that it relies on the proportion of time spent in each disease category without regard for the temporal pattern of any fluctuations. Despite this, unsupervised clustering accurately separated those in remission for $>80\%$ of the 6 months. It also enabled accurate sub-classification of those with active disease. If this could be replicated in a larger sample, an algorithm could be built into the TrueColours UC platform to enable improved disease pattern phenotyping.

The flare algorithm successfully identified those patients with disease exacerbations. Using this type of algorithm superimposed on the SCCAI symptom graph would better highlight those patients with unstable disease. It would also allow the possibility of providing a percentage time spent in flare. The algorithm (SCCAI $\geq 5$ for $\geq 3$ days AND an increase of $\geq 1$) functioned well, but a weakness of the approach used in this thesis is that the threshold deployed may be lower than some physicians may endorse. This algorithm could be adapted to other thresholds.
There was poor correlation between FCal and the SCCAI (rmcorr 0.311) but high correlation with UCEIS and Nancy (rmcorr 0.701 and 0.829 respectively), which is higher than in previously reported literature (244, 245). The largest separation in distribution of FCal values were achieved with a combined approach, using both UCEIS and Nancy criteria. This combined approach also achieved the lowest FCal cut-offs with the highest accuracy, sensitivity and specific of all criteria examined (86%, 85% and 89% respectively). When the strictest criteria of remission defined as UCEIS = 0 AND Nancy = 0 and active disease defined as UCEIS ≥4 AND Nancy ≥3 were applied, a FCal cut-off of 147 µg/g was found. This cut-off increased to 180 µg/g when the combined criteria were expanded for remission to include UCEIS 1 and Nancy 1, and active disease to include Nancy 2. This is clinically useful as it represents that if a patient has an FCal of <180 µg/g, they are likely to be in remission. This approach needs further validation, however FCal may act as a reliable marker of mucosal healing, potentially replacing the need for endoscopy in some patients.

The data on endoscopically and histopathologically defined remission and active disease was too small to draw any conclusions however the self-reported SCCAI appears to be more valuable than any of the laboratory measures. An increased sample size would allow a prediction model to be developed.

This chapter has emphasised the opportunity that real time data entry offers. The analysis of the TrueColours UC longitudinal repeated measures allowed in depth interrogation of symptom and QoL indices. A novel way to cluster patients by their disease patterns may assist in phenotyping patients accurately with the aim of enabling more homogeneous UC populations to be studied. The data on information loss will encourage us to create an algorithm that will result in maximal capture of disease exacerbations. The integration of a flare algorithm into TrueColours UC is possible allowing quantification of days spent in
disease exacerbation. Faecal calprotectin was shown to correlate poorly with symptoms, but well with endoscopy and histopathology. All of this encourages further TrueColours UC implementation.
Chapter Eight

Conclusions

8.1 Summary of this thesis

Ulcerative colitis (UC) runs a heterogeneous course. Tracking the disease through real time monitoring is not only useful within the clinical setting, but also allows a better understanding of disease patterns. The advent of the smartphone and other developments in e-health technology has made this possible.

The first half of the thesis (Chapters 1-4) focuses on the rationale behind real time monitoring, operation of the TrueColours software and feasibility of implementation. Chapter 1 places UC in a clinical context, emphasising the unpredictable disease course as well as the impact on both the patient and the health care system. The UK IBD Standards, which refer to patient-centred care, patient support and information technology, provide a rationale for real time monitoring in UC patients. The importance of links between e-health technologies and the hospital/clinic are highlighted, as well as an overview of current or emerging international IBD e-health programmes. The successful development of such programmes in the United States, the Netherlands and Denmark supports the value of real time monitoring in IBD. Programmes are to a large extent country-specific, since the value of e-health to patient management is generally contingent on and subject to the specific healthcare system of that country. No such programme for real time monitoring in IBD has been established in the UK, although TrueColours Bipolar, which has been used in clinical psychiatric practice in the Oxford region for almost a decade, provided a working platform that enabled adaptation. Chapter 2 describes the adaptation of TrueColours Bipolar to TrueColours UC. Multiple domains of disease activity were considered, as well as all indices for these domains. Reasons
for selection of indices for each domain are described. Novel features beyond the
TrueColours Bipolar platform, tailored the programme to UC, demonstrating the flexibility of
the TrueColours platform. The TrueColours platform can theoretically be adapted to any
chronic disease. It is the first e-health programme to collect internationally agreed patient-
reported outcome measures (PROMs) in IBD.

Chapter 3 examines the feasibility of implementing TrueColours UC using descriptive
analysis. Adherence rates to data collection through questionnaire completion were good
(daily average 76%, fortnightly average 95%) as was retention (86% at 6 months). Further
thought needs to be given to identifying eligible patients, improving recruitment and the
logistics of biological sample collection and processing. It is clear that patients on biological
therapy are most motivated to use TrueColours UC and these represent an initial target group
for implementation in a wider population.

Chapter 4 evaluates the usability of TrueColours UC using a mixed methods approach.
Usability, assessed quantitatively by the System Usability Scale, was very good (median
(IQR) of 92.5 (80,95)). Nevertheless, qualitative interviews identified improvements (such as
improvement in labelling of the graphs) that, if implemented, might improve the usability of
TrueColours UC.

The second half of the thesis (Chapters 5-8) focuses on the impact of TrueColours UC on
clinical care and research. Chapter 5 explores patient perceptions of TrueColours UC using
qualitative analysis through face to face, semi-structured interviews. Responses were
positive, with the central theme of empowerment emerging from the interviews. Subthemes
were increased awareness, control over decision-making, reassurance, communication and a perceived decrease in the burden of treatment.

Chapter 6 considers resource utilisation. A logistic regression model is developed to predict the likelihood of escalation of therapy. Examples of corresponding nomograms for variations of this model are described. Internal validation was performed however external validation will be necessary before implementation. These models present a way of evaluating disease-management algorithms that can be both personalised and automated.

Chapter 7 analyses the longitudinal repeated measurements collected by TrueColours UC. The symptom index (Simple Clinical Colitis Activity Index, SCCAI) and its descriptors are examined in detail with a focus on whether extraintestinal manifestations should be included in a disease activity index. Correlations between the SCCAI and Quality of Life (QoL) indices and between QoL indices is performed. Both disease-specific (IBD Control-8 and the Crohn’s Ulcerative Colitis Quality-8) and generic (EQ-5D-3L) indices are examined. Disease patterns are explored through the calculation of the percentage of time spent in each disease activity state (remission, mild, moderate, and severe) over the 6 month pilot. Frequency of real time data entry has previously been arbitrary, with each new e-health programme determining its own interval, without examining the impact of different intervals. Daily entries in TrueColours UC has enabled mathematical analysis through a simulation model to explore the impact of increasing the intervals between entries. A ‘flare’ algorithm is successfully superimposed on the SCCAI graph to calculate how many days a patient spends in a pre-specified level of disease activity. Finally, endoscopic and histopathologic definitions of remission and active disease are used to explore whether faecal calprotectin or bloods results could be used to predict disease activity.
8.2 Key Contributions

The key contributions of this thesis are:

- A technology driven approach to capturing PROMs
- A novel tool (the TrueColours UC programme)
- Formal evaluation of feasibility and usability, which no other IBD e-health programme has reported
- An in-depth analysis of the value of a system like TrueColours UC to patients in relation to their care
- Development of a novel predictive score to assess the probability that escalation of therapy will be advised at an outpatient appointment
- Longitudinal analysis of repeated clinical measurements
8.3 Discussion

This thesis contributes to understanding the value of e-health programmes for real time monitoring in chronic disease. A new e-health programme, TrueColours UC, was developed and formally evaluated. It is a technology that can be used in many ways: clinical monitoring, collating longitudinal repeated measurement data from multiple patients and possible improvement in resource utilisation.

TrueColours UC proved to be highly usable. More salient was the evidence that patients enjoyed using the programme, since it empowered them to become aware of their disease control and involved in their management. Good adherence to submission of PROM questionnaires and exceptionally high retention rates support patient enthusiasm for such a tool.

Resource utilisation is a priority within the all public hospital environments, with ever increasing demand on outpatient clinics. Initiatives to improve resource utilisation are being sought for many chronic diseases and electronic data collection of PROMs could be an effective way to achieve this goal. The infrastructure necessary to change care pathways requires careful planning, but measuring outcomes that matter to patients themselves seems essential if care is to be cost-effective.

The thesis presents novel work on the longitudinal analysis of repeated measurements in UC. The daily detail of the data collected allowed exploration of correlations and patterns of disease in a way that has previously not been possible. Clustering techniques and algorithms have been applied to these data from a pilot study that has enabled patterns to be identified and a predictive index for decision-making constructed. With a larger cohort over a longer
period, longitudinal analysis has the potential to develop decision-making algorithms that will allow care-pathways to be optimised and a platform through which the biology of UC can be explored.
8.4 Further work arising from this thesis and related programme of work

Five streams of future work have arisen from this thesis:

1. **Optimisation of TrueColours UC to create TrueColours IBD**
   
   This will involve incorporating the suggested changes on visual appearance (for example, improving the labelling of graphs and wording of questionnaires) and adding questionnaires for both CD and IBD-unclassified. Similar methodology for selecting the appropriate indices as for TrueColours UC will be followed. The Norman Collisson Foundation continues to support this work and a new Research Fellow has been appointed to begin in early 2018.

2. **Integration of TrueColours UC into the Academic Health Sciences Network (Oxford AHSN)**
   
   The primary aims are to introduce PROMs into routine clinical practice to improve care and to develop new care pathways that will allow optimisation of outpatient appointments. It is planned that TrueColours UC will be implemented in 5 clinical sites within the Thames Valley, initially for patients on biologies. To achieve this goal, a project management group with a Regional Lead Clinician and Network Manager is being assembled as a new Network within Oxford AHSN (Q3 2017). The group will include a patient representative, IBD specialist (medical/nursing) and an executive representative. A lead clinician will be identified at each hospital site, an educational package constructed for both patients and staff, and practical hands-on support through a research associate will be arranged.
3. **Facilitation of Research**

Accurate longitudinal phenotyping of patients allows fluctuation in disease activity to be studied. If these results are matched with date-stamped research samples for genomics (study of the genome), proteomics (study of the proteome) and metabolomics (study of the metabolome), this would be an invaluable resource. To pilot this process, metabolomics was chosen and a collaboration between TrueColours UC and the Pharmacology Department (Professor Daniel Antony and Dr Fay Probert), University of Oxford, has been established. Preliminary results that will be reported as a separate paper reveal significant difference in the plasma Nuclear Magnetic Resonance (NMR) metabolic profiles of patients with a UCEIS ≤3 compared with those with a UCEIS ≥4. Using the concentrations of plasma metabolites alone, an algorithm was produced that correctly identified which UCEIS group (≤3 vs ≥4) a patient was in with an accuracy of 77 ± 5%.

The metabolic profile also identified patients who are going to improve or deteriorate over succeeding months (defined as a negative or positive step of ≥1 in the UCEIS respectively), using their baseline metabolic profile, with an accuracy of 77 ± 3%. Metabolites responsible for discriminating mild from severe disease (lipoproteins, glucose, lactate, glutamine, and branched chain amino acids) were distinct from prognostic metabolites (lipoproteins, phenylalanine, and histidine). This preliminary data suggests that the NMR metabolic profile may be useful in determining the level of endoscopic activity and prognosis of UC.
4. **Implementation of TrueColours with established initiatives**

Approaches have been made to investigate whether TrueColours IBD can assist in disseminating data collection of PROMs. The International Consortium of Health Outcome Measures (ICHOM) and Industry have been approached. Conversations are in process as to how this may be possible.

5. **Grant applications for forthcoming NHS digital initiatives are being considered**

   Recently announced (Q2 2017) are
   
   a. Accelerated Access Review funding (£39M) to assess the benefits of new technologies that deliver benefits to patients and value to the NHS
   
   b. Digital Health Technology Catalyst funding (£35M) to develop digital technologies to be used by patients
   
   c. Pathway transformation Fund (£6M) to help NHS organisations to integrate new technologies into everyday practice

8.5 **Conclusions**

Real time monitoring has the potential to have a profound impact on the approaches to, delivery and monitoring of care. Although nascent, TrueColours UC offers a vision of how e-health technology might improve patient care in IBD, streamline the use of healthcare resources and create opportunities for mathematical or laboratory research.
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Appendices
Appendix A

TrueColours Ulcerative Colitis
Inflammatory Bowel Disease Service
Translational Gastroenterology Unit
John Radcliffe Hospital
Chief Investigator: Alissa Walsh
Email: tcuc@ndm.ox.ac.uk

Study Title: TrueColours Ulcerative Colitis: A Pilot Study Examining Real Time Data Collection in Patients with Ulcerative Colitis

Ethics Ref no: 16/SC/0103
Phase: Observational, Pilot Study
Date/Version no: 23.08.2016
Amendment no: 1

Chief Investigator: Dr Alissa Walsh
Investigators: Dr Satish Keshav
Dr Oliver Brain
Assoc Professor Holm Uhlig
Professor Alison Simmons
Professor Gary Collins
Professor Simon Travis

Sponsor University of Oxford

Funders: AbbVie Pharmaceuticals
Norman Collison Foundation
Buhlmann Laboratories

Signatures .......................................................... / /
Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

AMENDMENT HISTORY

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  14.1 Participant Confidentiality
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  14.3 Other Ethical Considerations
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15.0 Finance and Insurance
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*A flare is defined as an increase of the SCCAI ≥3 points with a total SCCAI ≥ 5 for over 3 consecutive days.*
### 3.0 ABBREVIATIONS

<table>
<thead>
<tr>
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<tr>
<td>AE</td>
<td>Adverse event</td>
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<tr>
<td>AR</td>
<td>Adverse reaction</td>
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<td>CI</td>
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<tr>
<td>CRF</td>
<td>Case Report Form</td>
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<td>CTRG</td>
<td>Clinical Trials &amp; Research Governance, University of Oxford</td>
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<td>GCP</td>
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<td>IBD</td>
<td>Inflammatory Bowel Disease</td>
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<td>NHS</td>
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<td>NRES</td>
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<td>PI</td>
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<tr>
<td>PIL</td>
<td>Participant/ Patient Information Leaflet</td>
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<td>QoL</td>
<td>Quality of Life</td>
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<td>R&amp;D</td>
<td>NHS Trust R&amp;D Department</td>
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<td>REC</td>
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<td>SCCAI</td>
<td>Simple Colitis Clinical Activity Index</td>
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<tr>
<td>SOP</td>
<td>Standard Operating Procedure</td>
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<td>UC</td>
<td>Ulcerative Colitis</td>
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<tr>
<td>UCEIS</td>
<td>Ulcerative colitis Endoscopic Index of Severity</td>
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4.0 BACKGROUND AND RATIONALE

Ulcerative Colitis (UC) is the most common type of inflammatory bowel disease (IBD), affecting around 146,000 people in the UK with an incidence of approximately 10 per 100,000 people annually. UC is a chronic condition that can occur at any age, but the peak incidence is in young adults between the ages of 15 and 25 years old. The condition is associated with significant morbidity and, if poorly controlled, can have substantial impact on an individual’s social and psychological wellbeing. UC usually follows a course of relapse and remission. A quarter of people with UC are admitted to hospital at least once and these people have a 40% chance of colectomy (major surgery involving removal of entire large bowel) during the course of their disease.

Current medical approaches focus on treating active disease to control symptoms, improving quality of life and maintaining remission. Treatment for UC includes a range of medications including aminosalicylates (ASAs, mesalazine, sulphasalazine, olsalazine), corticosteroids, immunosuppressants (azathioprine, mercaptopurine) and biological therapies (infliximab, adalimumab, vedolizumab). These treatments are often only moderately effective and the biologic agents are expensive.

Conventional management of UC focuses on assessment during brief clinic visits often weeks or months apart. Symptoms may wax and wane in the intervening period, more or less controlled by medication. As a consequence, treatment decisions for IBD are often reactive, based on patient recall of events and blood, stool or endoscopic biomarkers dissociated in time. For obvious reasons, this is a sub-optimal way managing or understanding the impact of relapsing and remitting inflammatory disease, any more than ‘hypertension clinics’ in decades past were effective at managing hypertension.

There is, therefore, a need to access data on symptoms in real time, to analyse information trends or establish thresholds and determine their relationship to objective markers of inflammation, which may in turn give an insight into the biology of the disease. The advent of contemporary technology and the widespread use of personal devices and “smart phones” has made this hitherto impossible work, possible. This project will adapt the established “True Colours” Monitoring System developed for managing bipolar disorder by the Oxford Department of Psychiatry to patients with UC, and relate it to biological measures of inflammation.

To see the completed adaptation to TrueColours Ulcerative Colitis, please refer to the TrueColours Ulcerative Colitis User Guide and TrueColours Ulcerative Colitis Online Tour for detailed information; a brief outline of the programme is given below.

TrueColours Ulcerative Colitis is an online symptom tracking programme that will help us learn more about how UC symptoms and quality of life (QoL) can change over time. Participants answer daily questions about clinical symptoms and fortnightly questions regarding QoL. Monthly home stool testing will be facilitated by using an already existing app called CalApp® through a portal called IBDoc®. This system will be securely integrated with TrueColours (see section 4.10 for further details).

Results from other tests such as blood tests, stool tests (calprotectin levels as measured by the laboratory ELISA), sigmoidoscopy and histology results will also be entered into the TrueColours system. As there will be no integration between TrueColours Ulcerative Colitis and the participant’s electronic record, these results will be entered manually by the TrueColours team.

Participants will have full access to their own profile. TrueColours data is stored on a secure NHS server. Patients can access their own record at any time via the website https://ouh.truecolours.nhs.uk/ibd
The TrueColours team will always be happy to help if patients have any difficulties or further questions about using the TrueColours system. The contact will be Dr Alissa Walsh at tcuc@ndm.ox.ac.uk. Dr Walsh will help to register all participants on the TrueColours system. After this initial step the participant will receive an email confirmation of the registration, including instructions regarding an initial password and logging in. If participants forget their password, they can request a new one by clicking ‘Forgotten your password?’ on the homepage.

Once registered, the participant will receive daily email prompts to complete a symptom (the ‘SCCAI’) questionnaire. All a participant needs to do is to click on the email link and this will take them directly to the symptom questionnaire. Completing the questionnaire will take less than 2 minutes. The answers entered relate to the 24 hours prior to the daily email prompt. This SCCAI evaluates a variety of symptoms such as stool frequency, rectal bleeding and incontinence so that a total daily score out of 19 can be calculated. Full details of the email prompt and subsequent steps can be found in the TrueColours Ulcerative Colitis User Guide.

Once a fortnight the participant will also be asked to complete three additional short questionnaires relating to quality of life. All of these questionnaires have been designed to be fast and convenient and will operate via the email prompt.

Participants can access their TrueColours record online at any time, by signing in to the secure TrueColours website: https://ouh.truecolours.nhs.uk/ibd

When participants log into the TrueColours they will see the dashboard that has been designed with the theme of traffic lights in mind.

The colour of the dashboard will change according to the patient’s current symptoms.

**Green** means there are few or no symptoms of colitis (SCCAI 0-5)

**Amber** means the symptoms are intermediate (SCCAI 6-11)

**Red** means that the symptoms are bad (SCCAI 12-19)

The colour that is on the dashboard relates to the last time questions were answered. Full examples of the dashboard, available tabs and functionality of the program are given in the TrueColours Ulcerative Colitis User Guide.

We believe that ulcerative colitis represents a paradigm for this real-time data approach: the disease usually affects a young and technologically literate patient population and is a frequently relapsing and remitting disorder. Furthermore, both patients and physicians recognise the need to change attitudes: clinical nurse specialists in IBD are a standard of care in the UK, (IBD Standards http://www.ibdstandards.org.uk/) which leads the world in this area, providing advice lines, telephone clinics and monitoring therapy in an endeavour to be create a more responsive service for patients. Other approaches have been subject to randomised controlled trials: guided self-management, and web-based management, both of which have proven successful. What is lacking is a functional tool.
Pivotal to the success of such a monitoring programme for UC are the patients themselves. The data clearly show that patients are keen to be involved in their own care. A survey of over 5000 patients in six European countries and Canada showed that 88% search online for information about IBD, most doing so several times a month (IBD 2020 survey www.ibd2020.org, presented to the EU Parliament 17 Oct 2013) and two thirds would be interested in using a mobile phone app to manage their IBD.

5.0 STUDY OBJECTIVES AND OUTCOME MEASURES

5.1 Primary Objective
To assess the feasibility of using TrueColours Ulcerative Colitis to collect real time data in patients with ulcerative colitis

5.2 Secondary Objectives
To correlate conventional markers of disease severity – symptoms, blood tests, stool tests with novel markers of disease activity
To understand facilitators and barriers of the uptake of TrueColours by patients

5.2 Tertiary objectives
To assess the usability of TrueColour Ulcerative Colitis

5.3 Primary Endpoints
- Percentage of days that SCCAI symptom questionnaire completed
- Percentage of fortnights that CUCQ8 quality of life questionnaire completed
- Percentage of fortnights that IBD Control quality of life questionnaire completed
- Percentage of fortnights that EQ-5D quality of life questionnaire completed
- Feasibility of assessment procedures (stool collection, sigmoidoscopy, blood tests, immuneprofiling)

5.4 Secondary endpoints
- To determine whether there is any preliminary signal from immuneprofiling
- Percentage of patients recruited after the invitation letter received
- Percentage of patients consented after having received full education and information regarding the study
- Percentage of patients who stopped using the True Colours system for over 1 month during the 6 month trial period
- Percentage of patients who chose to create a personalised questionnaire and subsequent adherence to answering this

5.5 Tertiary endpoints
- Exit (6 month) usability survey results - System Usability Scale (SUS)
- Exit (6 month) qualitative interview
6.0 STUDY DESIGN AND METHODOLOGY

The purpose of this external pilot study is to provide information for planning and justification for a randomised controlled trial that would examine efficacy. Because randomised controlled trials are costly and time consuming, major funding bodies require this evidence prior to funding approval.

6.1 Flow Diagram

7.0 PARTICIPANT IDENTIFICATION

7.1 Study Participants
The study sample consists of participants with a previous established diagnosis of UC (as per the European Crohn’s and Colitis guidelines). Eligible patients will be identified from those patients currently registered with IBD service at the Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford, UK. There are currently over 700 UC patients registered on the main IBD database (IBD Live) at the John Radcliffe Hospital. IBD Live is a clinical database for IBD patients and registration does include consent to be contacted regarding research studies (Clause 3 of Consent Form). This database can be used to identify patients. All patients have already been registered and have given written informed consent for the Oxford IBD database and tissue bank (Research and Development Reference: 5864, Research Ethics Committee Reference: 09/H1204/30, HTA 12217).

7.2 Inclusion Criteria
The following patients will be eligible for the study:
- Males and females aged 18-65 years
- Diagnosis of UC of any extent or severity
- The patient must have an email address
• Possession of a Smart phone and with regular internet access (A smart phone is a mobile phone with an advanced mobile operating system which combines features of a personal computer and can access the Internet, have a touchscreen user interface and can run third-party apps)
• Capacity to answer daily questions independently
• Provide written informed consent to participate as shown by a signature on the consent form.

7.3 Exclusion Criteria
The following patients will be excluded from the study:
• A diagnosis of Crohn’s Disease or indeterminate colitis.
• Planned extended (greater than 1 month) overseas travel if internet access will be impossible, inconvenient or unaffordable during this time.
• Previous colectomy for UC.
• Unable to communicate well with investigators or unable to comply with the study requirements

8.0 STUDY PROCEDURES

8.1 Recruitment
This pilot study will involve a maximum of 60 participants. The number of participants from each category of severity will be:

**Remission** (defined as SCCAI 0, 1, 2): 5 participants
**Active disease**: 55 participants in total. The active participants will be recruited in the following numbers:
- **Mild** (defined as SCCAI 3, 4, 5) 25 participants
- **Moderate** (defined as SCCAI 6, 7, 8, 9, 10, 11) 25 participants
- **Severe** (defined as SCCAI ≥12) 5 participants

Disease activity will be determined on the day of consent and registration. The duration of the study for each individual participant will be 6 months.

8.2 Screening and eligibility
There are two IBD clinics and multiple infusion appointments per week (for ulcerative colitis medications that require intravenous administration such as intravenous iron and biologic medications) at the John Radcliffe Hospital. Approximately 40 UC patients are seen each week at these clinics.

The clinical IBD team (IBD nurses and IBD physicians) will be responsible for checking the outpatient clinic lists and IBD Live for eligible UC patients. A letter will be sent to any eligible patients two weeks prior to their planned clinic visit to inform them of the TrueColours study. Please see the Patient Invitation Letter. Attached to this letter will be a copy of the Participant Information and a copy of the Consent Form and the TrueColours Ulcerative Colitis User Guide.

Patients who express interest in the study after receiving an invitation letter however who fail the inclusion/exclusion criteria, for example a patient who does not own a Smartphone or does not have access to the internet, will be informed that they are not eligible for inclusion into the study and will be treated by the IBD service as per standard clinical practice.

8.3 Informed consent
If a patient would like to participate they will be asked to give written informed consent. The participant must personally sign and date the latest approved version of the Informed Consent form before any study specific procedures are performed. All eligible patients who are willing to participate...
will be given the opportunity to ask questions, and will be thoroughly informed about the study before signing consent.

Written and verbal versions of the Participant Information and Informed Consent will be presented to the participants detailing the exact nature of the study; what it will involve for the participant; the implications and constraints of the protocol; any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study.

Written Informed Consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the Informed Consent. The person who obtained the consent must be suitably qualified and experienced, and have been authorised to do so by the Chief/Principal Investigator. A copy of the signed Informed Consent will be given to the participant. The original signed form will be retained in the hospital notes and another copy will be filed in the CRF.

Consent will also be obtained for a letter to be sent to the participant’s GP informing them of their patient’s involvement in the TrueColours programme.

8.4 Baseline education regarding TrueColours
Once written informed consent has been obtained, the participant will be given a one-on-one education session regarding TrueColours, receive another copy of the TrueColours User Guide and be shown the TrueColours Online Tour. The participant will have ongoing access (via the Help tab of the TrueColours programme) to this tour should they need to access it. Together with the education session, the participant should be well equipped on how to use of the TrueColours system. This process will be facilitated by Dr Alissa Walsh – an iPad and wifi will be available within the outpatient clinic/hospital to facilitate this process.

8.5 Registration with TrueColours
Following informed consent, the participant will then be registered with the TrueColours system. This registration will be performed by the TrueColours research team.

To register a participant the following steps are:
1. Login into website https://ouh.truecolours.nhs.uk/ibd
2. Enter username (this will be participant’s email address)
3. Enter password
4. Click on the ‘Caseload’ tab
5. At the top left corner there is a green box that says ‘+ new participant’. Click on this tab and enter all details. Those with an * are compulsory.
6. A page which says ‘Success’ will let you know that the new participant has been successfully added. Push ‘OK’.
7. Remain in the ‘Caseload’ tab
8. Select your patient from the list of patients
9. It will come up on the ‘Graph’ tab, please go to the ‘Schedules’ tab
10. Click on the green box which say to ‘Schedule a new questionnaire’
11. Choose a programme – in gastroenterology we only have TrueColours ulcerative Colitis at present so it will default to this. Push next.
12. Choose the SCCAI. Push next
13. Choose a start date and time. The time needs to be between 6am -10am and should be the patient’s choice. It is best to start the questionnaires on the following day. Push next.

14. The ‘Receive Prompts’ page will appear and the ‘send prompts’ box should be ticked. Push next.


16. The ‘End date’ page will appear. As this pilot study is running for 6 months please enter to end after 200 repeating periods. Push next.

17. You will then be shown a ‘Summary’

18. Please push ‘Finish’ if you are happy with the summary. If you are not happy with the summary, push ‘Back’ until you get to the page that allows you to fix the problem.

19. You will then be taken to the ‘Active Schedules’ page.

20. To schedule the quality of life questionnaires (CUCQ-8 and EQ-5D) please click ‘Schedule a new questionnaire’ at the bottom of this page.

21. At the programme page push next

22. Click on both CUCQ-8 and EQ-5D. Click Next

23. Follow all prompts as above with the only difference being that these need to be marked as fortnightly on the ‘Frequency of prompts page’. For the time of prompts, please ensure that this is at the same time of day as the SCCAI prompt so that all questionnaires can be filled out together on that particular day.

24. A summary will appear at the completion and if you are happy with this, please click on ‘Finish’.

25. The treatment guidance for each individual patient will need to be completed. A template is written out for each category (remission, mild, moderate and severe). Free text is needed to adjust this guidance. Once the physician is happy with each category it is approved. This is the information that will appear on the participant’s dashboard.

26. A copy of the template is as below. This is fully adjustable as to the patient’s needs and can be amended at any time by the TrueColours team. It cannot be amended by the participant themselves.

27. This registration will prompt an email to the participant and this then enrolls the patient in the TrueColours programme. All participant demographics will be available from the Oxford IBD database (IBD Live) – gender, smoking status, family history and medications and this information will be updated at the time of recruitment to ensure that it is accurate and current.
### Low Risk

#### Oral mesalazine:
If you have been in the green zone for over 3 weeks, decrease your mesalazine dose to 2-3g daily.

Mesalazine need only be taken once daily, whatever the dose.

Stopping mesalazine (or missing a dose more than once a week) is known to increase the risk of relapse by more than 5-fold.

#### Topical therapies:
(suppositories and enemas)
If you have been in the green zone for over 3 weeks, decrease your topical therapy to every 2 days for one week and then every 3 days for 1 week and then cease if bleeding has not returned.

#### Prednisolone:
Reducing your total exposure to prednisolone is very important to reduce short and long term complications.

If you are on prednisolone, please continue to wear your prednisolone as per your specialist team’s instructions.

#### Other therapies:
Please continue all other prescribed ulcerative colitis medications and do not change any of these doses without consultation with your specialist team. These medications will help keep you in the GREEN Zone.
Please record any changes in your medications.

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### Mid Risk

#### Oral mesalazine:
Increase/maintain your dose of mesalazine to 4-6g daily.

Mesalazine need only be taken once daily, whatever the dose.

#### Topical therapies:
This is an ideal time to focus on topical therapies. Start mesalazine suppositories 1 gram each night for 3 weeks.

If bleeding persists for more than 10 days after this, or if there is deterioration, then please contact your specialist team (link to phone or email). The aim is to get you into the GREEN zone, and if symptoms are improving, please continue the above treatment.

#### Prednisolone:
If you are on oral prednisolone please follow your specialist team’s instructions regarding the appropriate wearing protocol. Please do not start prednisolone without first speaking to your specialist team.

#### Other therapies:
Please continue all other prescribed ulcerative colitis medications and do not change any of these doses without consultation from your medical team. These medications will help you to enter the GREEN zone.
Please record any changes in your medications.
8.6 Email Prompts
Once enrolled in the TrueColours, the participant will receive daily email prompts to answer questions pertaining to their symptoms over the preceding 24 hours. This email link will take the participant directly to their questionnaire. The disease activity index that has been chosen is known as the Simple Colitis Clinical Activity Index (SCCAI) and components/questions include such things as frequency of bowel motions, urgency to defecation (whether the participant needs to rush to the bathroom), nocturnal diarrhoea (getting out of bed during the night due to requiring to pass a bowel motion), and faecal incontinence. This process will take less than 1-2 minutes to complete on a daily basis. The participant will be given the opportunity at registration to elect the best time to receive this prompt. If the participant does not reply to the prompt they will not be emailed until the following day, as per their normal email prompt.

Once these simple questions are completed a total score for the SCCAI (maximum score of 19) is calculated and this corresponds with the current activity of the participant’s disease. This is then translated to colours that correlate with a traffic light system (green: remission (0, 1, 2)/mild activity (3, 4, 5), amber: moderate activity (6, 7, 8, 9, 10, 11), and red: severe activity (≥12)) and a face with different expressions to correlate with disease activity. Please TrueColours Ulcerative Colitis User Guide and the TrueColours Ulcerative Colitis User Guide or Online Tour to see examples.

Participants will also receive fortnightly prompts regarding quality of life indices – Crohns Ulcerative Colitis Questionnaire–8, IBD Control and EQ-5D. For the fortnightly questionnaires, if no response is obtained, the participant is then prompted again the following day. If no response is obtained, the patient will not be prompted again until the next fortnight. The participant does have the opportunity to do a catch up survey if they wish by using the ‘Questionnaires’ tab on the main dashboard.

For personalised questionnaires, if the patient wishes to temporarily stop their personalised question prompts, they need to select ‘Suspend schedule’. Alternatively, the patient can go to the questionnaires tab by signing in to TrueColours at https://ouh.truecolours.nhs.uk/ibd. If they would prefer not to receive email prompts for their personalised questionnaires they can uncheck the box next to the text ‘Please send prompts to remind me’ (see TrueColours User Guide for more details).
8.7 Personalised Medication Guidance

At the time of registration, Dr Alissa Walsh (who is an experienced consultant gastroenterologist), in consultation with the treating IBD team will enter treatment guidance for each patient for each colour category. This treatment guidance works from a template (see above in Section 4.7), however this will be individualised for each patient and so can take into account past history and any intolerances. For example, please see the screenshot immediately below. The individualised treatment guidance for this participant asks the participant to increase the dose of their oral mesalazine (a current medication) and to start mesalazine suppositories (a medication that is used on an intermittent basis). These medications will be very familiar to the patient.

![Screenshot showing personalized medication guidance](image)

Treatment guidance will be limited to topical (rectal) therapies and oral aminosalicylate use. This guidance will be tailored to each participant. It is important to note that for reasons of safety, for participants who are either currently on or considering commencing immunomodulators or biologic therapy, they will not receive advice via TrueColours in relation to these medications.

8.8 Other Investigations

8.8.1 Blood

Blood tests will be collected at enrolment, monthly, and at times of a flare, and at exit from study at 6 months.

Due to the variety of routine clinical care pathways in this patient population, it will not be possible to align all research procedures with routine care visits, however, we will endeavour to do so where possible. Arrangements have been made to reimburse participants for transport to research visits when no routine visit will take place.

A **flare** is defined as an increase in symptoms rather than an absolute SCCAI value. An increase in the SCCAI of ≥3 points with the absolute SCCAI level being ≥5 for ≥3 days.

Blood will be tested for Full Blood Count, Iron studies, C-Reactive Protein and Albumin. This blood will be processed with patient details and will be fully available on the hospital pathology system. These results will be entered manually into the CRF in a de-identified manner as well as the TrueColours programme by the TrueColours research team.
To enable us to research the biology of ulcerative colitis extra blood (approximately 50ml) will be taken. These samples will be held in a linked anonymised form. Blood will be separated to generate peripheral blood mononuclear cells and plasma. Some whole blood will be used to make and store DNA. This will all be held in a secure laboratory on the 5th Floor Nuffield Department of Medicine.

Immuneprofiling, a generic term that describes the analysis of blood biomarkers of immune pathway activation, offers the opportunity to link fluctuation in clinical disease activity to the biology of disease. It is hoped that this will help stratify patients and their likely response to potential treatments. At present biomarkers consist only of tests that reflect inflammation in a crude or non-specific manner (eg C-reactive protein or calprotectin); nevertheless, these are already in use clinically to guide treatment decisions, since immunosuppressive therapy is generally started or escalated when such markers confirm that symptoms are due to active inflammation.

Following completion of the project, any surplus participant blood samples from those participants who have consented for these samples to be used by the Inflammatory Bowel Disease in Oxford Prospective Cohort (REC Ref: 09/H1204/30, HTA 12217), will be kept in a secure laboratory on the 5th Floor Nuffield Department of medicine.

Should participants refuse to allow samples to be stored at the completion of the study they will be destroyed at the end of the study.

8.8.2 Stool
A baseline Faecal Calprotectin will be tested by the IBD Clinic as per normal clinical practice. Home stool test kits for faecal calprotectin (IBDoc®) will also be provided to TrueColours patients upon enrolment, to be used on a monthly basis. The purpose of these stool kits is to evaluate inflammation (via a calprotectin level) in the bowel via a stool sample. The value of this test is that it can be done in the privacy of one’s own home. The results of the calprotectin level will be incorporated into the patient’s TrueColours record and will be graphed in a similar manner to symptoms and quality of life. The IBD service at the John Radcliffe Hospital is not routinely using this home kit however many sites in Europe are using the home test as part of their standard normal care. The home stool kits are being provided for the TrueColours programme by BÜHLMANN.

It is important to note that BÜHLMANN does not see any data of doctors or patients. BÜHLMANN only see the contact information of the clinical administrator (the same as the patient sees) and can be given access to anonymised results by the clinical user. The data belongs to the TrueColours programme and not to BÜHLMANN. Certain data is stored on servers located in the European Union (but outside the UK). User access to the IBDoc® Portal and CalApp® is login and password protected. Access to data is restricted depending on the user level. TrueColours will be the administrator and Dr Alissa Walsh will be the clinical user for the purposes of this project.

The TrueColours team will do the following:
1. Agree terms and conditions with local BÜHLMANN representative (Distributor)
2. Sign up for IBDoc® account. TrueColours is the owner of data of that account.
3. TrueColours will create a “clinic” on the IBDoc® portal and all participants in the TrueColours programme will be added to this portal at the time of consent and registration.
4. Edit the clinic information visible to participants and BÜHLMANN will create and manage Clinical Users (which in this case will all be listed under Dr Alissa Walsh)
5. Edit and access Patient User administrative information
6. Create and manage the Patient (Participant) User. This will require entry of patient initials, date of birth and the email address that the participant has chosen to use for this project.
7. A patient ID will be an automatically generated number allocated by the portal when a new patient is created.
8. Edit medical information. The test frequency (monthly) & result classification (for this project it will be quantitative as well as colour coded (green, amber, red). That is, participants will be given their actual numerical result of their calprotectin level.

9. A message will be sent to the participant (via email) when the home stool test is due.

10. TrueColours only (and not BÜHLMANN) can see results of assigned participants. Overdue tests will be seen on the IBDoc® portal (that only the TrueColours research team can access for the clinic created) and can be followed up by email by the TrueColours team.

The participant in the TrueColours programme is:
1. Created by the TrueColours research team after informed consent is received.
2. Required to access the app. The participant will need to download the IBDoc® app called the CalApp® and is downloaded free: iTunes App store for iPhones 32.7MB. Google play store for Android phones – 18MB.
3. Will be able to see their own results. An individual participant cannot see any other participant’s results.

The app only functions after login with a user name and password. Password is obtained after the Clinical user (Dr Alissa Walsh) creates a Patient User. The CalApp® downloads and uploads data to the IBDoc® Portal through a secure shell, SSH connection (256 bit encryption). Participant results are uploaded to the IBDoc® Portal only with an accompanying participant ID: participant’s initials + unique identifier, as a sole source of patient identification.

Once downloaded, the app (see below) will ask for an email address and ask the participant to sign up for an account. The participant will need to provide the TrueColours team with an email address that they are going to use. Once entered onto the system a message will be sent with a link for you to set the password. This needs activating within 24 hrs (can use the ‘forgotten password’ link to reset). If not received check the Spam folder to ensure it hasn’t been caught.
**IBDoc® Portal**

The IBDoc® Portal web interface to server and server to server communication is using a 256 bit Secure Socket Layer (SSL) protocol using TLS 1.2 and AES_256_CBC encryption standard with HMAC-SHA1 for message authentication and ECDHE_RSA as the key exchange mechanism.

Sensitive data fields are encrypted using a 256 bit AES key using the keyczar cryptographic toolkit (https://github.com/google/keyczar).

Master, slave and back up server are located in three geographical separate data centers. The master server is synced to the slave every 5 minutes. Back up snapshots are taken every 4 hours from the slave server and stored on a separate back up server. The last 6 snapshots are kept 24 hrs, one daily snapshot is kept 7 days, one weekly snapshot will be kept for 30 days.

In case master server and slave server both fail and cannot be recovered, the system can be restored with a maximum of 4 hours of data loss. Tests performed by patients are stored locally on the phone and sent to the server once a connection is established. Potential loss of results is therefore minimal. The servers have a guaranteed uptime of 99%. Due to support and maintenance reasons the server can be taken offline but cumulative time will not exceed more than 15 minutes per calendar month.
BÜHLMANN support retains contact information of the clinics and can only access anonymised results after given explicit permission by Clinical User. A scenario where this may occur is if there was an unexpected result and the TrueColours programme was questioning the result. For example if a very clinically well participant (with low symptom scores) has a high calprotectin result, the result may need to be questioned.

Each participant will need to receive the following:
1. TrueColours needs to be given to each participant and education session to fully understand how the home testing process works.
2. A set of test kits will be supplied free of charge to each participant. The number supplied will depend on their next planned visit to the hospital and storage capacity in their home fridge.

Performing a Test
The following information will be explained to the participant.
1. The IBDoc® kit needs to be stored in the fridge (none of the components are poisonous).
2. Remove the kit from the fridge when you are going to perform a test and keep at room temperature until needed (do not return the cassette to the fridge).
3. A camera test is performed using the card in the IBDoc® kit.
4. The camera test lasts for 30 days.
5. If the camera test fails: repeat in good light (no flash), ensure phone case is not obstructing, clean the lens and try again.
There is a quick pictorial guide (this can be skipped if not required):

6. A picture speaks a thousand words – encourage participant to watch the video https://www.youtube.com/watch?v=38p0zuQUCWY&feature=player_embedded.
7. The bladder should be emptied first as urine can dilute the result if mixes with stool and urine will also weaken the collection paper.
8. Ideally encourage collection of the first stool of the day as this has the highest level of calprotectin.
9. Open the collection paper carefully otherwise it is liable to tear.
10. The collection paper will not stick to the porcelain, only the toilet seat.
11. Pass a bowel motion onto the collection paper.
12. Remove the white cap and collect the sample by dipping the sampling pin into the faeces and twisting. Repeat this process 3 – 5 times so the grooves are filled.

13. Stool consistency: It is best if completely liquid stools are not used but if only liquid stool is available then this is better than having no test at all. Do NOT sample from mucoid areas – this will cause lower results. Hard stools are difficult – use something to trap the stool against and push the CALEX into the sample.
14. Do NOT wipe any excess faeces from the end of the sample tip – this has been factored in. Put the sample pin back into the tube, you will hear and feel two clicks, shake and then leave the CALEX.

15. Leave the CALEX valve at room temperature, away from direct sunlight and upright so that the solution covers the end of the sampling pin. Leave for between 2 and 24 hours for the calprotectin to dissolve into the solution.

**After 2-24 Hours, NEXT STEPS**

1. Make sure you leave sufficient time to perform the test – especially the first few times. Do not rush.
2. Log into the App first – if you have forgotten your password it will take longer than 12 minutes to get a new one sent.
3. Shake the CALEX briefly - you may see debris in the solution. This is fine, as long as there is no faeces stuck to the grooves in the sampling pin.
4. Only open the test cassette when you are ready to do the test – once opened it needs to be used within 4 hours otherwise moisture will influence the test.
5. Flick the CALEX tube to release air bubbles before removing the blue cap.
6. Open the CALEX lever only once.
7. Remove the blue cap, and ensure the CALEX is in position over the cassette before opening the lever otherwise some fluid may be lost.
8. Apply the liquid into the circle at a slight angle to allow for better release of the liquid.
9. Wait until the reddish line is half way up the test window before removing the CALEX.
10. Start the timer (12 minutes).
11. After 12 minutes, put the cassette on the blue reverse side of the camera test card.
12. Hold the camera level over the cassette – it will automatically focus and read the result.
13. Comments can be added to the result using the ‘Notes’ box e.g. sample consistency.
14. Save, and the result will be sent to the portal.
15. Dispose of the CALEX valve and the test cassette.
8.8.3 Endoscopy
Routine care now recommends endoscopic confirmation, according to international STRIDE guidelines. Participants will also be asked to have a sigmoidoscopy within 14 days of enrolment and at 6 months (completion of the study). Due to the variety of routine clinical care pathways in this patient population, it will not be possible to align all research procedures with routine care visits, however, we will endeavour to do so where possible. Arrangements have been made to reimburse participants for transport to research visits when no routine visit will take place.

If participants have a flare (see above definition) of disease and have not had a sigmoidoscopy within 4 weeks of that flare, the clinical team treating the participant will offer another sigmoidoscopy, as part of routine care, to further assess extent and activity of disease so that medication can be optimised.

The endoscopic appearance will be scored by the treating endoscopist using the Ulcerative Colitis Endoscopic Index of Severity (UCEIS) and the Mayo Endoscopic Index and these scores will be entered into the system manually by the TrueColours research team. Biopsies will be taken as per normal clinical practice and additional a maximum or 8 additional biopsies will be taken for research purposes. The number of additional biopsies will be limited by the number required clinically.

For most biopsies, these will be taken, digested and utilised within a week with no remaining material stored. In some cases biopsies will be fixed and stored for the duration of the study.

Following completion of the project, any surplus participant tissue samples from those participants who have consented for these samples to be used by the Inflammatory Bowel Disease in Oxford Prospective Cohort (REC Ref: 09/H1204/30, HTA 12217), will be kept in a secure laboratory on the 5th Floor Nuffield Department of Medicine.

Should participants refuse to allow samples to be stored at the completion of the study they will be destroyed at the end of the study.

8.8.4 Histology
Histological scoring will be routinely scored to assess severity and this result will also be entered by the research team into the TrueColours Ulcerative Colitis programme.

8.9 Qualitative Interviews
Towards the end of the 6 month pilot period, a proportion of participants will be invited to take part in a face to face interview. There are no specific inclusion/exclusion criteria for this voluntary interview however purposive sampling will be used to ensure that a balanced sample (age, gender, disease activity, adherence to the TC programme) is achieved. Participants will be provided with a dedicated interview “Patient Information Sheet” and will be required to sign an additional consent prior to the interview. All interviews will be conducted by Dr Alissa Walsh, Chief Investigator. All interviews will be recorded and professionally transcribed. We will endeavour to align the interview with a routine care visit. Arrangements have been made to reimburse participants for transport to research visits when no routine visit was required. It is proposed that each interview will be approximately 30 minutes however this will depend on how much feedback the participant has to offer.

8.10 Sample handling
For bloods and tissue samples collected as part of the participants routine care, all results will be available to both the participant’s clinical team and the TrueColours research team on the hospital pathology system.
The participant will also be assigned a study number for the CRF and research samples. This study number will be used to label all research bloods and tissue samples. This study number will be documented next to patient name and date of birth and hospital number in the securely kept master file so it will be re-identifiable by the TrueColours research team.

Following completion of the project, any surplus participant samples from those participants who have consented for these samples to be used by the Inflammatory Bowel Disease in Oxford Prospective Cohort (REC Ref: 09/H1204/30, HTA 12217), will be kept in a secure laboratory on the 5th Floor Nuffield Department of Medicine.

Should participants refuse to allow samples to be stored at the completion of the study they will be destroyed at the end of the study.

8.11 Discontinuation/Withdrawal of Participants from Study
Each participant has the right to withdraw from the study at any time. In addition, the Investigator may discontinue a participant from the study at any time if the Investigator considers it necessary for any reason including:

- Significant non-compliance with treatment regimen or study requirements
- Withdrawal of Consent
- Loss to follow up
- Colectomy performed for medically referactory disease

The reason for withdrawal will be recorded in the CRF.

If a participant withdraws from the study, they will have the option of allowing the TrueColours Research team to use the clinical data and samples up until the date of withdrawal or to have their TrueColours file and samples deleted.

To delete a participant from the TrueColours programme completely, this needs to be done manually through the TrueColours support team (contact Christopher Hinds, email chris.hinds@psych.ox.ac.uk or Ash Wadekar, vanashree.wadekar@psych.ox.ac.uk).

To destroy blood or biopsy samples, this will be arranged through Dr Alissa Walsh, the CI, who will identify the participant’s sample number and arrange for these samples and any data pertaining to these samples to be destroyed.

If a patient does withdraw from the study, another patient may be recruited.

8.12 Definition of end of study
The end of study is the date of the 6 month exit sigmoidoscopy or qualitative interview (whichever comes last) for the last participant.

9.0 SAFETY REPORTING

This is a pilot study of TrueColours Ulcerative Colitis. The aim is to track symptoms and quality of life and faecal calprotectin in real time. Treatment guidance regarding topical (rectal) medication and oral aminosalicylates are given as outlined above. No advice pertaining to immunosuppressant medication or biologics are given. The patient is prompted to contact the IBD unit if their symptoms are deteriorating or if they need further advice. Contact details are clearly displayed.
Normal standard of care will apply to all participating patients. No new medications are being studied and therefore we feel that general safety assessments such as vital signs and additional physical examinations are not necessary. Blood tests, sigmoidoscopy and histology results will be monitored as per our normal standard of care for any patient in the IBD service.

Definition of Serious Adverse Events
A serious adverse event is any untoward medical occurrence that:
- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- consists of a congenital anomaly or birth defect.

Reporting Procedures for Serious Adverse Events: A serious adverse event (SAE) occurring to a participant should be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website).

Serious Adverse Event Collection Period: Serious related adverse events occurring from the time of initiation of True Colours UC will be reported until the last visit of the last participant, at which point the intervention is concluded.

In the event of a serious adverse event the member of the care team who detects the event will notify the Chief Investigator on the same day as he or she becomes aware of the event. Preferred method of reporting by email: tcuc@ndm.ox.ac.uk as well as a phone call to Dr Alissa Walsh on +44 7495920267.

10.0 STATISTICS AND ANALYSIS

10.1 Description of Statistical Methods
Given that this is a pilot study analysis will be mainly descriptive. It is expected that data from a maximum of 60 patients will be collected. As data is being collected on a real time basis, no entry into a central database will be necessary.

10.2 The Number of Participants
No formal sample size has been performed for this pilot study however we feel that 60 patients will allow us to examine all of the primary and secondary endpoints. This will then allow us to ensure that the programme itself, education, registration procedure and additional resources are in place. It will also assist us in performing a sample size calculation for a larger trial.

10.3 Analysis of Outcome Measures
Both distributions and descriptive statistics of both central tendency (medians and arithmetic or geometric means) and dispersion (standard deviation, interquartile range) will be presented for quantitative variables. Nominal variables will be described with frequencies, percentages and modes, while ordinal variables will also have medians and interquartile ranges described. Analysis of the qualitative interviews be assisted by the NVivo program.
11.0 DATA MANAGEMENT

11.1 Access to Data
Direct access will be granted to authorised representatives from the Sponsor, regulatory bodies and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

11.2 Data Recording and Record Keeping
Security of data collection, handling, transfer, storage and use is a key component of the chronic disease cohorts in Oxford and central to the continuing integrity and viability of the research projects.

For this study, most of the data is entered directly into the Truecolours system by the participant themselves – this includes all data in the questionnaires apart from the exit usability questionnaire which will be answered on a paper copy and will be an anonymous survey.

The recorded qualitative interviews will be transferred to the professional transcriber as secure files. The recording will be transferred to a secure NHS computer as soon as possible after the interview and the interview will then be deleted from the recorder. The file will be identified with the participants TC number rather than the participant’s name. Instructions will be given to the transcriber to delete any names from the transcription and a contract will be signed with the transcriber to ensure that all information is kept confidential. When the transcripts are re-read by Chief Investigator, Dr Alissa Walsh, she will also ensure that no patient identifiers are present. The electronic, re-read copy of the transcript will be then be used for analysis.

The home stool testing results will also be transferred to the TrueColours programme as described in section 8.8.2.

Each participant will have a CRF. This will be labelled with their initials and date of birth and TrueColours Study Number. In this CRF will be de-identified results from blood tests, sigmoidoscopy and histology results. These results will subsequently be entered into the participants TrueColours profile by the TrueColours research team. The CRFs will be kept in a secure locked office with limited access at the Translational Gastroenterology Unit, John Radcliffe Hospital.

A separate master file will be kept in a locked filing cabinet in the same office. This file will have a full copy of all study documents (protocol, PIS, Consent, Invitation letter etc) as well as a list participants full details, corresponding study number and completed consent forms. Study number will be assigned to participants on a consecutive basis TCUC001, TCUC002, TCUC003, etc.

Access to the TrueColours programme is username and password locked and so only members of the TrueColours Research team will have access to participant information.

Study participant’s TrueColours profile will remain on the server for 3 years after study completion. The files will then be batch deleted.

The CRFs and master file will be kept for 3 years at which point they will be destroyed.

12.0 QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.
13.0 ETHICAL AND REGULATORY CONSIDERATIONS

13.1 Declaration of Helsinki
The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

13.2 Guidelines for Good Clinical Practice
The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

13.3 Approvals
The protocol, informed consent form, participant information sheet will be submitted to an appropriate Research Ethics Committee (REC), and host institution for written approval. The Investigator will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

14.0 REPORTING

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, host organisation and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

14.1 Participant Confidentiality
The data for TrueColours will be hosted on a secure NHS (OUH) server. The HTTPS protocol is used for secure communication of data. Access to the data from the website is restricted by the user role. For example a clinician will be able to see data only for their participants and participants can only see their own data. All data are encrypted. All users require names and passwords to access their data. All published data will be anonymous.

The integration of IBDoc® and TrueColours will be through application programming interface (API). There is a dedicated API server (EU) which will allow server to server communication. There will be no app to app communication.

It is important to note that Buhlmann (owner of CalApp) does not see any data of doctors or patients. Buhlmann only see the contact information of the clinical administrator (the same as the patient sees which in this instance will be the TrueColours Research Team) and can be given access to anonymised results by the clinical user. The data belongs to the TrueColours programme and not to Buhlmann. Certain data is stored on servers located in the European Union (but outside the UK).
User access to the IBDoc® Portal and CalApp® is login and password protected. Access to data is restricted depending on the user level. Please see section 7.8 for more details.

Data from the qualitative interviews will be kept confidential as described in Section 11.2.

A separate master file will be kept in a locked filing cabinet in the same office. This file will have a full copy of all study documents (protocol, PIS, Consent, Invitation letter etc) as well as a list of participants’ full details, corresponding study number and completed consent forms.

A researcher with access to the master list will be responsible for adding all test results (identified by the participant ID #) to the TrueColours system. Only researchers who are appropriately trained will have access to this data and the system and subsequently all hard copies will be stored separately to identifiable information as explained above.
14.2 Expenses and Benefits
The benefit of such a system is potentially significant from both a patient care perspective and a
clinical/disease insight perspective. We believe this tool will be easily usable, feasible and that it will
allow the biology of the disease to be followed for the first time.

TrueColours will be provided to the participant free of charge. The participant however will need to
have their own email/Smart phone/computer and have their own internet access. Website access is at
the participant’s own expense. The cost is dependent on an individual’s internet service provider or
wireless access via their mobile carrier.

Home stool kits (Faecal Calprotectin) to be performed on a monthly basis (or more frequently if a
patient’s symptoms increase) will be provided to the participant free of charge. These kits have been
provided by Bulhmann Laboratories. See section 7.8 for full details of the integration with
TrueColours.

All equipment used for blood and stool pathology and endoscopy is as per standard practice and
normal clinical care. SomaLogic/immuneprofiling testing of frozen plasma will be at no cost to the
patient.

Should no routine visit be required by the participant, we will request they attend for the research
procedure only. In these circumstance we will reimburse the participant for their travel on production
of valid receipts.

14.3 Other Ethical Considerations
Risks to the individual participant are limited. There is the potential for technological issues with the
system such as server downtime or errors in the data capture process, however the TrueColours
system has been successfully used in Psychiatry, Neurology and Orthopaedics with no major issues to
date. If there were issues with the system this would mean that the patient’s data may not able to be
entered for that period of time however we do not believe that this would place the patient at risk.

Possible misunderstanding of the medication guidance. This guidance has therefore been limited to
aminosalicylates, topical (rectal) therapies and decreasing corticosteroid exposure. There is a low risk
of an adverse event from an increase in dosage of 5-aminosalicylic acid as suggested in the treatment
guidance if a patients symptoms were increasing. Reactions to 5-aminosalicylic acid are often not
dose related and most participants will have been exposed to these medications in the past. There is
no risk of increasing topical (rectal) medication.

There is a potential risk (1 in 8000) of damage to the bowel (perforation) or bleeding at the time of
sigmoidoscopy. The sigmoidoscopies for this study will be performed on dedicated Inflammatory
Bowel Disease Consultant lists. These consultants are highly experienced in investigating and
managing ulcerative colitis.

In order to minimise burden on participants we will align research visits with routine care where
possible.

14.4 Current legal provisions
In accordance with the UK Department of Health Research Governance Framework for Health and
Social Care this type of study, except in specific cases, must be submitted for review by an
independent committee. This study will therefore be submitted for review by an NHS Research Ethics
Committee, via the National Research Ethics Service.
Trust management approval for local conduct of the study will be sought via the Research and
Development (R&D) department.
15.0 FINANCE AND INSURANCE

15.1 Funding
Funding for TrueColours Ulcerative Colitis has been received by
1. Norman Collison Foundation: 106,000 GBP
2. Abbvie Pharmaceuticals: 68,000 GBP
3. Buhlmann Laboratories: full supply and delivery of all IBDoc home test kits.

15.2 Insurance
The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd’s of London). NHS indemnity operates in respect of the clinical treatment that is provided.

16.0 PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by the Norman Collison Foundation, Abbvie Pharmaceuticals and Buhlmann Laboratories. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

TrueColours Ulcerative Colitis will be submitted as a DPhil in Clinical Medicine at the University of Oxford. At the end of the study, a study report will be written by the chief investigator who will also sign the report. This report will be very detailed and will contain a description of the objectives of the study, the methodology of the study and its results and conclusions. All participant data included in publication will be anonymous. Specifically, any quotes that will be used in reports or papers will be fully anonymised.
# Appendix B

## Simple Clinical Colitis Activity Index (SCCAI)

<table>
<thead>
<tr>
<th>Descriptor</th>
<th>Description</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bowel frequency (day)</td>
<td>0-3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>4-6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>7-9</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>&gt;9</td>
<td>3</td>
</tr>
<tr>
<td>Bowel frequency (night)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>1-3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Urgency of defecation</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Hurry</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Immediately (toilet nearby)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Incontinence</td>
<td>3</td>
</tr>
<tr>
<td>Blood in stool</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Trace</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Occasionally frank (&lt;50% of defecation)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Usually frank (&gt;50% of defecation)</td>
<td>3</td>
</tr>
<tr>
<td>General well being</td>
<td>very well</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>slightly below par</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>poor</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>very poor</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>terrible</td>
<td>4</td>
</tr>
<tr>
<td>Extracolonic features</td>
<td>1 per manifestation Arthritis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Uveitis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Erythema nodosum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Pyoderma gangrenosum</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Total (out of 19)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Appendix C

IBD Control Questionnaire

![IBD Control Questionnaire Image]

Note: The IBD Control-8 questionnaire is taken from the following questions:
1a, 1b, and 3a to 3f
Each question is scored as follows
0 = worst response (that is either a ‘Yes’ or ‘No’ depending on the question – should be obvious which)
1 = intermediate/indeterminant (= ‘Not Sure’)
2 = best response (that is either a ‘Yes’ or a ‘No’ depending on the question – should be obvious which)

1a Yes=2, No=0, unsure=1
1b Yes=0, No=2, taking no therapy=1
3a to 3f Yes=0, No=2, unsure=1

So if all responses are favourable then 8 x 2 = 16, equivalent to best control
Appendix D

Crohn’s Ulcerative Colitis Questionnaire-8 (CUCQ-8)

The following questions ask for your views about your bowel problem and how it has affected your life over the last two weeks.

Please answer all the questions. If you are unsure about how to answer any question, just give the best answer you can. Do not spend too much time answering, as your first thoughts are likely to be the most accurate. If you do not wish to answer any of these questions, please leave it blank and complete the details of the question and reason(s) why it was not answered.

1. On how many days over the last two weeks have you felt tired? ………….. days

2. In the last two weeks did your bowel condition prevent you from going out socially?
   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

3. On how many days over the last two weeks have you felt generally unwell? ………….. days

4. On how many days over the last two weeks have you felt pain in your abdomen? ………….. days

5. On how many nights in the last two weeks have you had to get up to use the toilet because of your bowel condition after you have gone to bed? ………….. nights

6. On how many days over the last two weeks has your abdomen felt bloated? ………….. days

7. In the last two weeks have you felt upset?
   a) No, not at all
   b) Yes, some of the time
   c) Yes, most of the time
   d) Yes, all of the time

8. On how many days over the last two weeks have you had to rush to the toilet? ………….. days

If you did not complete any of these questions, please record the question number(s) below and, if possible, give a reason why it was not completed

# Appendix E

## Ulcerative Colitis Endoscopic Index of Severity (UCEIS)

<table>
<thead>
<tr>
<th>Descriptor (Score most severe lesions)</th>
<th>Likert Scale anchor points</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular pattern</td>
<td><strong>Normal (0)</strong></td>
<td>Normal vascular pattern with arborisation of capillaries clearly defined, or with blurring or patchy loss of capillary margins</td>
</tr>
<tr>
<td>Patchy obliteration (1)</td>
<td></td>
<td>Patchy obliteration of vascular pattern</td>
</tr>
<tr>
<td>Obliterated (2)</td>
<td></td>
<td>Complete obliteration of vascular pattern</td>
</tr>
<tr>
<td>Bleeding</td>
<td><strong>None (0)</strong></td>
<td>No visible blood</td>
</tr>
<tr>
<td>Mucosal (1)</td>
<td></td>
<td>Some spots or streaks of coagulated blood on the surface of the mucosa ahead of the scope, which can be washed away</td>
</tr>
<tr>
<td>Luminal mild (2)</td>
<td></td>
<td>Some free liquid blood in the lumen</td>
</tr>
<tr>
<td>Luminal moderate or severe (3)</td>
<td></td>
<td>Frank blood in the lumen ahead of endoscope or visible oozing from mucosa after washing intra-luminal blood, or visible oozing from a hemorrhagic mucosa</td>
</tr>
<tr>
<td>Erosions &amp; Ulcers</td>
<td><strong>None (0)</strong></td>
<td>Normal mucosa, no visible erosions or ulcers</td>
</tr>
<tr>
<td>Erosions (1)</td>
<td></td>
<td>Tiny (&lt;5mm) defects in the mucosa, of a white or yellow color with a flat edge</td>
</tr>
<tr>
<td>Superficial ulcer (2)</td>
<td></td>
<td>Larger (&gt;5mm) defects in the mucosa, which are discrete fibrin-covered ulcers when compared to erosions, but remain superficial</td>
</tr>
<tr>
<td>Deep ulcer (3)</td>
<td></td>
<td>Deeper excavated defects in the mucosa, with a slightly raised edge</td>
</tr>
</tbody>
</table>

*UCEIS® copyright is registered to Watson Laboratories, Parsippany NJ, United States a subsidiary of Actavis Inc., as successor in interest of Warner Chilcott and Procter & Gamble (“Licensor”), on the principle that there is unrestricted access to the UCEIS®.

Appendix F

Nancy Histological Index


(Permission obtained for reprint from Laurent Peyrin-Biroulet).
Appendix G

TrueColours Ulcerative Colitis
Inflammatory Bowel Disease Service
Translational Gastroenterology Unit
John Radcliffe Hospital
Chief Investigator: Alissa Walsh
Email: tcuc@ndm.ox.ac.uk

Invitation Letter

TrueColours Ulcerative Colitis: a pilot study examining real time data collection in patients with ulcerative colitis

Date: Rec Reference 16/SC/0103
Dear ……………
You have an appointment at the Inflammatory Bowel Disease Clinic at the John Radcliffe Hospital in several weeks. We would like to invite you to be involved in an exciting new research project called TrueColours Ulcerative Colitis.

This is an online web-based platform whereby we can track your symptoms in “real time” – by using your smart phone or computer. It would involve you entering your symptoms each day. You will need to have your own smart phone to participate. Your symptom information would then be available to both you and the TrueColours team.

We are investigating the changing patterns of ulcerative colitis and we are hoping to find out more about why symptoms flare up. This programme will also alert you to worsening symptoms at an earlier stage. We have included a copy of the patient information, consent form and a Help Guide to give you a better idea of what the programme is.

You will be approached at your clinic appointment to discuss your interest in participating. Education regarding the programme, registration and consent would take an extra hour of your time.

If you would like to ask further questions regarding what would be involved prior to your appointment, please email tcuc@ndm.ox.ac.uk and we will arrange to speak with you. We are aiming to enrol approximately 60 patients into the programme. Participation is entirely voluntary.

Kind regards

Dr Alissa Walsh and Professor Simon Travis
Translational Gastroenterology Unit, John Radcliffe Hospital, Oxford
Appendix H

TrueColours Ulcerative Colitis
Inflammatory Bowel Disease Service
Translational Gastroenterology Unit
John Radcliffe Hospital
Chief Investigator: Alissa Walsh
Email: tcuc@ndm.ox.ac.uk

Patient Information Leaflet

TrueColours Ulcerative Colitis: A pilot study examining real time data collection in patients with ulcerative colitis

You are being invited to take part in a clinical research study carried out by the Gastroenterology Unit at the John Radcliffe Hospital and the University of Oxford. This study forms the basis of a doctoral thesis for the University of Oxford. Before you decide whether or not you wish to take part, you should read the information provided below carefully and, if you wish, discuss it with your family, friends or GP. Take time to ask questions – do not feel rushed or under any obligation to make a hasty judgement. You should clearly understand the risks and benefits of participating in this study so that you can make a decision that is right for you – this process is known as ‘Informed Consent’.

You are not obliged to take part in this study. You may change your mind at any time, before the start of the study or even after you have commenced the study, for whatever reason, without having to justify your decision. This too will have no negative impact on the care you receive.

What is the purpose of the study?
Despite encouraging advances in the understanding of ulcerative colitis (UC), the illness continues to cause debilitating ill-health, and treatment often remains unsatisfactory. The Gastroenterology Unit at the John Radcliffe Hospital have already performed extensive research that has enabled us to understand UC better. This study is a feasibility study of a monitoring procedure. It aims to establish whether it is possible to obtain a detailed record of your symptoms and quality of life using this new technology. An additional aim is to try to link these fluctuations in symptoms with markers of disease through examining stool inflammation markers, blood samples and biopsies. We hope that this will help us to further understand UC and lead to advances in management.
Why have I been invited?
We are offering participation to patients with UC who attend the Inflammatory Bowel Disease outpatients clinic at the John Radcliffe Hospital and for this pilot study a maximum of 60 patients will be recruited. Participation in this study will be for 6 months.

Do I have to take part?
No. Participation is entirely voluntary. If you do decide to participate you can withdraw from the study at any stage without giving any reason. Withdrawal from this study will not affect your clinical care.

What will happen to me if I decide to take part?
TrueColours is a secure online system which requires you to enter your symptoms on a daily basis. Over time the programme collects all of the information that you have entered and graphs the changes in your symptoms. This information is able to be viewed by yourself and the TrueColours research team. All information that you enter will be confidential but will not be anonymised. Certain blood test results such as blood results, sigmoidoscopy results and histology results will also be entered onto the system. Home stool kits to measure faecal calprotectin (a surrogate marker of inflammation within the bowel) will also be made available to you.

All study participants receive the same programme. Once you register with the TrueColours programme you will receive daily email prompts to answer a questionnaire related to your current ulcerative colitis symptoms. This will take less than a minute to complete. You will also receive a fortnightly email prompt to answer a questionnaire related to your quality of life. If you do not respond to the fortnightly email within 24 hours a reminder email will be sent to you. These questionnaires can either be answered on your smartphone or on your computer. Your information will be username and password locked.

A daily symptom score will be calculated and some treatment guidance will also be offered depending on the severity of your current symptoms. This treatment guidance will be individualised to you at the beginning of the study and can be further customised at any stage if needed.

You will be given an education session and a booklet that explains how to use the TrueColours programme and the TrueColours team will be easily contactable if you are experiencing any difficulty with the programme. Initial education and registration will take between 30-60 minutes. If you agree to participate, we will record your TrueColours entries on a secure NHS server and we will also enter your routine blood, stool, sigmoidoscopy and biopsy results.

Your treatment will continue as before, and will be entirely governed by your clinical needs. You will continue to be seen by the same team of doctors and nurses, in the outpatients department or ward exactly as before - participation in TrueColours will be in addition to the routine practice of having your clinical details maintained in the medical notes and on the hospital computer.

In addition, we will be asking your permission to take, store, and use some samples of blood, stool, and tissue. We will use the blood and stool samples to analyse chemicals, proteins, and cells to look at how your immune system is working. We will also look for markers of inflammation. Some of this blood will also be used process and store your DNA. These results will not be available on the TrueColours system.

Blood samples
As part of this research, we will request blood samples from you once per month. We will be recruiting a variety of patients with UC. Some patients will already be having monthly blood tests. We would then ask for an extra sample (around 50ml or about three tablespoons). For patients who do not have blood samples regularly, we would still ask for a sample of about 50ml once per month. We
will contact you to make an appointment and will pay any travel expenses upon production of receipts.

The blood tests will test for things such as your Full Blood Count and C-reactive protein (CRP) and will be processed in the hospital laboratory. These results will be manually entered into your de-identified study file and then into your TrueColours profile by the research team.

The extra 50ml of blood that we will take is for research purposes. As well as examining your immune system to check for any markers to help us understand why ulcerative colitis flares up, we will use the blood to look at your genetic information to determine which, if any, of the known genes involved in IBD are altered in your case. These research sample will be labelled with a study code (rather than your name) and so the research laboratory staff will not know who which patient the sample has come from. This code can be linked back to your name by the TrueColours research team after the research analysis has taken place. Also, because you DNA is unique to you it can never be completely anonymous. None of the research results of this optional blood sample will be entered onto your TrueColours profile.

**Stool samples**

Upon entry to the study, we will ask for a sample of stool. We will give you containers to catch the stool. You can take the containers away with you and bring the samples when you next attend the hospital.

The TrueColours programme has been given access to some home stool testing kits which will enable us to monitor inflammation in the bowel by testing a marker called ‘calprotectin’. We will teach you how to use these kits and will ask you to perform these home tests on a monthly basis if your symptoms are stable and more frequently (up to weekly) if your symptoms are increasing. Using this kit will involve going through a stepwise protocol, a brief outline of which is displayed below.

The kit must be kept in a fridge. Its use involves your passing a bowel motion on to a piece of collection paper, then using a dip stick to take a sample and transfer this to a vial. The vial is left at room temperature for between 2 and 24 hours to dissolve the sample. Analysis of the dissolved sample takes around 15 minutes. This involves using a dip stick to transfer some of the sample to a test cassette, waiting 12 minutes, then using the CalApp to read and record the result. The CalApp will use your smartphone/tablet camera to read the result. All the necessary kit will be provided and the procedure carefully explained to you.

**Intestinal tissue samples**

To enable us to get a full and accurate view of your current disease activity we ask that you have a sigmoidoscopy within a few weeks of enrolment in the study and at 6 months, upon completion of the study. This procedure is very common and will be carried out to the usual NHS standards. If you have a routine hospital appointment, we will try to coincide with this. If you are not visiting the hospital, we will arrange an appointment with you and pay any travel expenses you incur. Being part of this study will mean that you will be asked to have at least 2 sigmoidoscopies within a 6-month period. One of these sigmoidoscopies is in addition to standard care.

If your symptoms flare within the 6-month trial period a sigmoidoscopy may also be required at that time, but this will be determined by your treating team. If you require this procedure due to a symptom flare, routine biopsies will be taken as part of your normal care. We will ask your permission to take and store additional small samples of your intestinal tissue for the research. Your clinical biopsies would be given priority and we would only take additional research biopsies if it was safe and appropriate to do so.

Your samples may be used to perform specialist tests to examine ‘gene or protein expression’. This examines how active a gene or protein may be and how genes and proteins that control inflammation may be affected in UC. We do this to help understand the role of different genes within the body and
how they may lead to the development of UC. It is unlikely there will be any implications for yourself or your family and therefore we will not be feeding back the specific results of these tests.

**Treatment Guidance**

Treatment guidance will be limited to topical (rectal) medication and oral mesalazine and this guidance will be individualised to your particular situation. For other medications that you may be taking or considering starting for your UC, the IBD team will liaise with you directly regarding these, as per your routine care.

**Follow up**

Your progress will be carefully monitored and if you are experiencing any issues with the TrueColours system or require advice this will be readily available. After your 6-months has been completed you will be asked to complete an exit questionnaire which will help us to assess the usability of the TrueColours system. This questionnaire will be anonymous and will give us valuable feedback on the programme. Your care will continue in the IBD clinic as per normal and there will be no interruption to care.

**What will happen to the samples I give?**

Once the analysis is performed on your samples, these results will be correlated with your TrueColours profile to see whether we can see a pattern between your symptom fluctuations and the expression of different proteins or the genetic markers in your DNA.

The blood and tissue samples will be stored in a secure laboratory at the John Radcliffe Hospital. Your blood and tissue samples will be assigned a code and your data will also be identified only by this number. The material that is used for this research will not have information that identifies you. In addition, we will also ask your permission to store the remainder of your blood samples as well as any intestinal tissue specimens that are taken as part of the research in our Inflammatory Bowel Disease biobank. This will enable your blood and intestinal samples to be used in future ethically approved studies of your condition.

These samples are also kept in a secure laboratory at the John Radcliffe Hospital. Storage of your samples for future studies is entirely voluntary. You may still participate in the study if you do not want your samples stored for future use. In this case we would destroy all samples within the compulsory one year period.

If you give your permission to store your samples in the Inflammatory Bowel Disease biobank for future related ethically approved studies in UC, as with the TrueColours study we will continue to remove your personal details from all research samples so that they are all anonymous. All specimens will be carefully catalogued and maintained in a facility which is fully compliant with the requirements of the Human Tissue Act.

**What should I consider?**

To participate in the TrueColours study you will require a Smartphone and regular internet access. The TrueColours programme is only available in English at this stage. If you are actively involved in another clinical trial at present it may not be suitable to also be involved with TrueColours.

**Are there any possible disadvantages or risks from taking part?**

The additional risk in taking part in the study, over and above the risks associated with standard treatment of Inflammatory Bowel Disease, is low.

As we will be collecting and storing large amounts of data, it is possible a breach of confidentiality could occur, in order to minimise this risk, the TrueColours programme sits on a secure and dedicated NHS server. Only you and the TrueColours team can access your data and all entry to the site is username and password locked. Your home stool testing results will be securely held on the IBDoc portal under the TrueColours name with the only access to these being yourself and the TrueColours research team.
Extra blood taken at the time of your blood tests or in some cases additional blood tests will be required. There are minimal risks related to obtaining the blood sample. Some individuals may experience tenderness, a small bruise or possibly fainting.

Extra biopsies at the time of your sigmoidoscopy or in some cases an additional sigmoidoscopy will be required. Most people experience no adverse effects as a result of a sigmoidoscopy. The most common adverse effects are abdominal discomfort at the time of the procedure. This discomfort generally settles either immediately or within an hour of the procedure. On extremely rare occasions, the procedure is associated with more serious complications. There is a very small risk of (less than 1 in a thousand) bleeding or of making a hole in the bowel (perforation), which may require surgery.

The questions asked in the questionnaires are very similar to questions that are asked in the clinic setting and are unlikely to cause any distress. There may be some minor discomfort in having blood taken including the possibility of bruising and/or fainting.

**What are the possible benefits of taking part?**
TrueColours will allow you to monitor your own progress. Guidance on your management will be personalised to you. You will gain access to the home stool testing kits that will allow both you and us to track the inflammation in your bowel.

**Will my General Practitioner/family doctor (GP) be informed of my participation?**
If you agree we would like to inform your GP that you are participating in this study. We will provide your GP with a letter that briefly explains the TrueColours study and documents your participation.

**Will my taking part in the study be kept confidential?**
Your information will be kept entirely confidential. The data for the TrueColours programme will be hosted on a secure NHS (Oxford University Hospital) system. The HTTPS protocol is used for secure communication of data. Access to data from the website is restricted by the user role. The only people who will have access to your TrueColours profile will be yourself and the TrueColours research team. Access to the TrueColours system is username and password access only. No other patient will be able to access your data and you will not be able to access other patients’ data.

In order to perform the home stool testing you will be required to download an app to your mobile phone or tablet called ‘CalApp’. This app securely adds your test results to the TrueColours system via an ‘IBDoc’ clinic’ and a server based in the EU. All data is encrypted. The company who facilitate CalApp and IBDoc do not have access to your results unless the TrueColours team needs further assistance with a sample and in this instance a query will be sent in an anonymised fashion.

Your email address is required for registration with the app, however, nobody outside the research team will be able to see any other personal information about you or any of your test results. All paper study documentation will be kept in two secure files. The first file is a coded (de-identified) file of your blood, endoscopy and histology results which will subsequently be transcribed by the research team into your TrueColours profile. The second file will hold a list of participant names, study numbers and signed consent forms. These files will be kept in the same secure office however the file with your actual name will be kept in a locked filing cabinet.

Responsible members of the University of Oxford, Oxford University Hospitals NHS Foundation Trust and the appropriate Regulatory bodies may be given access to data for monitoring and/or audit of the study to ensure that the research is complying with applicable regulations.

**Will I be reimbursed for taking part?**
There is no financial benefit from participating in this study. If your blood tests or sigmoidoscopy appointments do not align with your clinical visits (that is, if this requires an extra visit to the hospital), your travel costs will be reimbursed upon issue of valid receipts.
You will need to have regular internet access to participate in this study and this cost (purchase and ongoing fees of the phone or internet) will be your responsibility through your normal contract with the provider. Home stool kits will be provided free of charge.

**What will happen if I don't want to carry on with the study?**
Withdrawal will not affect the care that you receive from the Inflammatory Bowel Disease service. If you withdraw from the study, unless you state otherwise, any details regarding symptoms and quality of life, blood or tissue samples which have been collected whilst you have been in the study will be used for research as detailed in this participant information sheet. You are free to request that your TrueColours data, blood or tissue samples are destroyed at any time during or after the study. Three years after study completion your TrueColours file will be deleted.

**What happens at the end of the study?**
A report or publication will be placed in the public domain at the completion of the study. These results will also be presented at both national and international conferences. You will not be identifiable in any of these reports or presentations. A report will be generated at the completion of the study and will be distributed to all participants.

**What if there is a problem?**
The University of Oxford, as Sponsor, has appropriate insurance in place in the unlikely event that you suffer any harm as a direct consequence of your participation in this study. NHS indemnity operates in respect of the clinical treatment which is provided.

If you wish to complain about any aspect of the way in which you have been approached or treated during the course of this study, you should contact Dr Alissa Walsh, email: tcuc@ndm.ox.ac.uk or you may contact the University of Oxford Clinical Trials and Research Governance (CTRG) office on 01865 572224, or the head of CTRG, email ctrg@admin.ox.ac.uk.

The Patient Advisory Liaison Service (PALS) is a confidential NHS service that can provide you with support for any complaints or queries you may have regarding the care you receive as an NHS patient. PALS is unable to provide information about this research study. If you wish to contact the PALS team please contact 01865 221473 or email: PALSJR@ouh.nhs.uk.

**How have patients and the public been involved in this study?**
Several patients have already piloted TrueColours Ulcerative Colitis. The True Colours programme has also been used in psychiatry, neurology and orthopaedics and these studies are ongoing. Patient feedback was integral in the design of TrueColours and we are hoping to make further adjustments at the completion of this pilot study after further feedback is received.

**Who is organising and funding the study?**
The study is being organised through the Gastroenterology Unit at the John Radcliffe Hospital. The Principal Investigators, listed above, are all consultant specialists in Gastroenterology. The project is funded by the Norman Collison Foundation, an independent charity, with separate support from industry (AbbVie and Bulhmann Laboratories) through unrestricted grants and supplying of equipment. No funding body have any input into the design, conduct, or outcome of the study.

**Who has reviewed the study?**
This study has been reviewed and given favourable opinion by South Central – Hampshire B Ethics Committee Research Ethics Committee.

**Further information and contact details:**
If you have any further questions about this project, you can talk to any of the research team, including the doctors, research fellows, IBD Specialist Nurse, and IBD Research Nurse. For additional information now or at any future time please contact:
Appendix I

TrueColours Ulcerative Colitis
Inflammatory Bowel Disease Service
Translational Gastroenterology Unit
John Radcliffe Hospital
Chief Investigator: Alissa Walsh
Email: tcuc@ndm.ox.ac.uk

Consent Form

TrueColours Ulcerative Colitis: a pilot study examining real time data collection in patients with ulcerative colitis

Principal Investigators: Dr Alissa Walsh, Professor Simon Travis, Dr Satish Keshav, Dr Oliver Brain, Professor Gary Collins, Professor Alison Simmons. Oxford Radcliffe Hospitals NHS Trust and University of Oxford

Ethics committee number: 16/SC/0103

Patient identification number for this study:
Thank you for reading the attached information sheet about our research project. If you would like to take part, please read and sign this form, and initial the boxes as indicated below.

1. I confirm that I have read the attached information sheet on this project, Version 3.0 dated 21/03/2016, and have been given a copy to keep. I have been able to ask questions about the project and have had these answered satisfactorily I understand why the research is being done and what, if any, risks are involved. 

2. I understand that the research team may want to access information about me that is held by the NHS and in my medical records. I give permission for authorised individuals to have access to my records where it is relevant to this research.

3. I understand that relevant sections of my medical notes and other data collected during the study may be looked at by individuals from the NHS Trust, Sponsor or from regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.
4. I understand that I will be entering data into a secure web based programme called TrueColours Ulcerative Colitis. This system is username and password locked. I will only have access to my own information. The TrueColours research team will also have full access to my information. This data is not anonymised but will be kept confidential.

5. I understand that the home stool testing will require me to download the CalApp® and that a programme called IBDoc® will be used to process this data. This data will then be securely transferred to my TrueColours file. The only people who can see my stool results are myself and the TrueColours team. The company who facilitate CalApp® and IBDoc® do not have access to my results unless the TrueColours team needs further assistance with a sample and in this instance a query will be sent in an anonymised fashion.

6. I agree for blood, stool and intestinal samples to be collected and I consider these samples a gift to the University of Oxford and I understand I will not gain any direct personal or financial benefit from them.

7. I understand and agree that my samples will examine my DNA for genetic factors in my condition.

8. I understand that the TrueColours research team are using any sample that I give to carry out research aimed at understanding the genetic and other influences and factors relevant to ulcerative colitis, but that the results of these investigations are unlikely to have any implications for me personally.

9. I agree to my GP being informed of my participation in this study.

10. I agree to take part in the above study.

11. OPTIONAL: Any unused samples that remain after the TrueColours research has been completed can be stored in the Inflammatory Bowel Disease tissue bank at the John Radcliffe Hospital, Oxford (REC 09/H1204/30, HTA License: 12217) for use in future research. These samples will be completely anonymous to the researchers.

   Yes  No

Participant Name:  Signature:  Date:

___________________  ____________________  ____________

Person Taking Consent:  Signature:  Date:

___________________  ____________________  ____________

When completed: 1 for participant, 1 for researcher site file and 1 (original) for medical notes
A User Guide to

True Colours

Ulcerative Colitis
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Introduction
In this guide you will find out how to use TrueColours Ulcerative Colitis, and how to understand your TrueColours record.

What is TrueColours?
TrueColours is an online symptom tracking system that will help us learn more about how your symptoms change over time. TrueColours will also allow you to monitor your symptoms and quality of life. You will have full access to the data you submit. We hope that you may also find the system helpful to see how your symptoms change over time. Results from other tests such as your blood tests, stool tests and sigmoidoscopy will also be entered into the TrueColours system.

Your TrueColours data is stored on a secure computer system. You can access your record at any time via the website https://ouh.truecolours.nhs.uk/ibd

You will receive an email with an initial password and instructions for logging into TrueColours. If you forget your password, you can request a new one by clicking ‘Forgotten your password?’ on the homepage.

Contact us
The TrueColours research team will always be happy to help if you have any difficulties or further questions about using the TrueColours system. If you do have questions, please contact Dr Alissa Walsh at tcuc@ndm.ox.ac.uk.

How to get started
Using TrueColours is easy. We will help you to register on the TrueColours system. After this you will receive a registration email confirmation, including instructions for logging in.
Completing your questionnaires
Once registered, you will receive daily email prompts to complete a symptom (the ‘SCCAI’) questionnaire. All you need to do is to click on the email link and this will take you directly to the symptom questionnaire (the ‘SCCAI’). This will take less than 2 minutes of your time. The answers that you enter on the symptom questionnaire relate to the 24 hours prior to the email prompt. Once a fortnight you will also be asked to complete two additional short questionnaires: these relate to your quality of life. All questionnaires have been designed to be fast and convenient.

How to access your TrueColours record
You can access your TrueColours record online at any time, by signing in to the secure TrueColours website: https://ouh.truecolours.nhs.uk/ibd
Tabs

Dashboard
When you log into TrueColours you will see the dashboard that has been designed with the theme of traffic lights in mind.

The colour of your dashboard will change according to your symptoms.

**Green** means you have few or no symptoms of colitis.
**Amber** means you have intermediate symptoms.
**Red** means that your symptoms are bad.

The colour that is on your dashboard relates to the last time you answered the questions.
Here are some examples of three different colours.

An example score in green:

![Dashboard with a green score of 3 indicating almost clinical remission.](image)

In this example, someone has a low score of 3 on their daily questionnaire. This indicates that their symptoms are few, so the dashboard appears green, with a smiley face.

An example score in amber:

![Dashboard with an amber score of 6 indicating active colitis.](image)

This example shows someone with a score of 6 on their latest questionnaire. The dashboard is amber indicating intermediate symptoms of active colitis.
An example score in red:

This example shows someone who has scored 12 on their latest questionnaire. The dashboard is red with a sad face because their symptoms are bad.

At the time that you register into the system, your IBD team will enter treatment guidance for each colour category. This treatment guidance will be personalised to you.

For example, if you were in green and then symptoms worsened to amber then treatment advice may appear as above.
Graphs
The graphs will map out your daily symptom scores, your fortnightly quality of life scores and some of your laboratory results.

The ‘Graph’ tab displays all of your scores for all of your questionnaires over a period of time. Symptoms (the ‘SCCAI’) are in purple, quality of life (the ‘CUCQ8’) is in aqua and a different quality of life score (the ‘EQ-5D’) is in brown. It will take a month or so before you have enough information on your TrueColours graphs to see patterns or changes in your scores.

You can use the grey tool box next to the graph to change the timescale on your graphs allowing you to view information on the graphs for longer or shorter periods of time. You can also specify a start and finish date for your graph if you are wanting to look at a specific time period.

You may wish to print a paper copy of your graphs which you can do by simply clicking on the ‘Print graphs’ button at the bottom of the grey box.
New
Under the “New” Tab there are 4 options: Questionnaires, Medication, Notes and External Inputs

Questionnaires
TrueColours will automatically send you an email prompt everyday. This email contains a secure link to your questionnaires. Clicking on the link will take you directly to the questionnaires.

To answer the questions all that you need to do is to choose the best response and then push the ‘Next step’ button.

When all of the questions are complete you will need to push the ‘Submit response’ button.
The ‘Questionnaires’ sub-tab also allows you to view the questionnaires at any time. Most of the time you will answer your questionnaires via the email link however if you would like to do any extra questionnaires go to the ‘New’ tab and then choose the ‘Medications’ sub-tab. Then click on the green button of the questionnaire that you would like to complete. You can also set up your own personalised questions (for example if you were wanting to monitor your exercise or adherence to medication).
Medications
The Medications sub-tab allows you to keep an updated list of your medications. Go to the ‘New’ tab and then choose the ‘Medications’ sub-tab. This tab allows you to enter your current ulcerative colitis medications and any changes to these medications.

![Medications sub-tab](image)

Notes
The ‘Notes’ sub tab allows you to add your own comments to TrueColours. Go to the ‘New’ tab and then choose the ‘Notes’ sub-tab. if you would like to add notes about things that may have changed your symptoms. For example, this may be medication changes, holidays, food or stressful life events. These will then appear on your graph so that you can monitor the effect on your symptoms.

To add a note, click on the green button that says ‘Add a new note’.

TrueColours will ask:
- What is your note about? You can decide the title of the note and this will appear in the ‘Notes’ box.
- You can add further information and details about your note.
- All of your notes will be available for you to view.
- The notes you add to your graph are not individually monitored in any way although they may be used for research purposes.
**External Data**

This is where your stool home kit (calprotectin) information is accessed. Please click on the ‘New’ tab and choose the ‘External Data’ sub-tab.
**Contact us**
You can contact the TrueColours IBD team via the ‘Contact us’ tab. Please use this tab if you would like further assistance with using the TrueColours system. If you are needing to speak to the IBD team urgently, please phone us as you normally would rather than sending an email. The best contact number for the IBD team is the help line: 01865 228772.

**Settings**
On the ‘Settings’ tab, you will be able to change the email address that your TrueColours prompt emails are sent to. Put your new email address in the ‘Please send emails to’ field and click save changes.

You can provide us with alternative email addresses that you can log in with, but you will not receive TrueColours prompt emails to these accounts. Only email addresses in the ‘Please send emails to’ field will receive TrueColours prompt emails.

You can change your password at any time on the settings tab.
Help
The ‘Help’ tab gives you access to a copy of the TrueColours Ulcerative Colitis User Guide as well as the TrueColours Online Tour.
What happens to your responses?
Your responses to each question are calculated to give you a total score for each time point on all questionnaires. These scores are then plotted on to your graph. For example when you have been using TrueColours for some weeks, your symptom graph (the ‘SCCAI’ graph) may look something like this:

- Along the horizontal line are month and date, moving from left to right.
- The vertical line shows the total scores for the questionnaire. On the symptom (‘SCCAI’) graph, higher up means a higher score. The worst score that you can get is 19 and the best score is zero.
- The purple line shows your total score from the SCCAI questionnaire over time.
- When the coloured line goes up, this shows that you have scored higher on the SCCAI (that is, your symptoms are worse).
- The example above shows a graph for an individual who has answered their symptom (‘SCCAI’) questionnaire for several weeks. You will notice that their highest score was at the beginning of January and their scores became lower over time, with their lowest score towards the end of February, meaning that their symptoms were improving.
Underneath the line graph is a picture that shows how you scored on each of the items in the symptom (‘SCCAI’) questionnaire. The larger the circle, the higher you scored on a particular symptom. For the example below look at the area marked with a red box. In this area the worst symptoms were frequency at night and blood in the stool. The way you can tell this is that the dots were larger for these two symptoms.
Personalised Questionnaires

How to create personalised questionnaires
You have the opportunity to create personalised questions. These allow you to monitor things that are important for you, such as exercise, dietary triggers or sleep.
On the ‘Questionnaires’ sub-tab (under the New tab), click on the green button to create a personalised questionnaire (you may need to scroll to the bottom of the page).

You can add up to 10 weekly and 10 daily questions. Choose whether you would like to add a daily or weekly question. Click on the green button to add a question.
Categories of personalised questionnaires
There are several categories with prewritten questions that you can choose from. By clicking on the category, a number of examples will appear. For example, the category ‘Anxiety’ has been selected in the image below.
If you would like to add the question, click ‘choose this question’.
Prompt times
After you have chosen a personalised question for the first time, you will be asked to specify a prompt time, you can change this to any time of your choosing.
Creating your own daily and weekly personalised questionnaires

You have the opportunity to make up your own question if there is something specific you wish to monitor. If you would like to make up your own question, select the button ‘No thanks—I’ll make up my own question’ at the bottom of the page.

As below, TrueColours will ask ‘What is the question you would like to ask yourself?’ . When typing your question into the box, TrueColours provides an instant preview of your question. You can then choose what kind of answer you will be giving. See the example below:
Once you have added your personalised question(s), TrueColours will then take you back to the personalised questions page showing your new questions.

On this tab, you can:

- Change your **prompt time(s)**
- View **details** of your personalised question(s).
- Add **new** personalised questions
- Delete personalized questions

If you wish to update your prompt time, you can do this by changing the time displayed under ‘Schedule’, then click ‘Update Schedule’.

If you wish to temporarily stop your personalised question prompts, select ‘Suspend schedule’, you can then resume the questionnaires at a later date.
Responding to your personalised questionnaires
TrueColours will email you a link to complete your questionnaires. Alternatively, you can go to the questionnaires tab by signing in to TrueColours at https://ouh.truecolours.nhs.uk/ibd If you would prefer not to receive email reminders for your personalised questionnaires you can uncheck the box next to the text ‘Please send prompts to remind me’ (see the image above).

Personalised questionnaire graphs
Once you have responded to your personalised questionnaire, this will be plotted on a graph on the ‘Graph’ tab. You can see your personalised questionnaire graph(s) alongside the graphs of other questionnaire(s) you are monitoring.

During the past week, how many alcoholic drinks have you had on a typical day?

What happens if I do not reply?
If you do not update your record following a daily prompt the system will have no record of your responses for that day and it will appear as a grey ‘x’ on the symptom graph. You will receive a prompt on the following day as per the usual process. The prompt that is received for symptoms always relates to the 24 hours before the actual prompt.

If you do not respond to the fortnightly quality of life prompts, you will receive a reminder 24 hours later. As the fortnightly questionnaires are further apart there is more opportunity to catch up if they are missed on the allocated day. If you do not respond to your reminder before your next prompt is due, it will appear as a grey ‘x’ on the symptom graph.

If you do miss your questionnaires for a day or so, please do not worry. Just continue on to the next day and answer your questionnaires for that day as normal.

Important notes
Website access is at participants’ own expense. The cost is dependent on an individual internet service provider.
Replies to the questionnaires and notes added to TrueColours are sent to a secure computer system for use in research purposes only. Responses are not individually monitored in any way.

If you require medical help, or are worried about your symptoms, it is important that you contact your healthcare professional through your normal route.
Appendix K

TCUC QUALITATIVE INTERVIEW
22/08/2016, Version 1.0

Notes to interviewer – Assuming AW to be performing all interviews

Greeting
As you may already know, I am an Australian Gastroenterologist and my main role at present is for my PhD of which the focus is the TrueColours program. Although there are many IBD doctors at the JRH there is a chance that I could be involved in your ongoing care. The main focus of this interview will be to focus on the TrueColours program. There are no right or wrong answers and your feedback is very valuable to me with the main aim of making TrueColours as good as it can be.

I want to let you know that
• Anything you say in this interview will be confidential. It is for research purposes only and will not be recorded in your medical file.
• You can withdraw at any point without giving a reason.
• I am interested to hear what you think about the TrueColours programme. There are no right or wrong answers. I am interested in what you think as it will help to improve the programme.

REMINDEERS
• Use participant’s own language and refer to specific health conditions they bring up in questions
• take participants’ cues around what affects them most and concentrate on most impactful conditions.
• Pay attention to emotion, repetition, personal stories, hesitations/broken speech, vivid descriptions as these may all indicate salience/importance of a particular area of discussion, or may indicate areas of particular sensitivity – prompt and explore sensitively and with an eye to identifying what the underlying impact on the person is

Thank you so much for your time today.
Your feedback regarding the TrueColours program is very valuable to us.
You have been using the TrueColours program for approximately 6 months.
One of the main purposes of this study is to see whether patients like this programme and how easy it is to use.

Do you have any questions before we begin?

Please remember that you are free to stop at any time. If at any point, you would like to stop, let me know.

If you don’t want to answer any of the questions that’s fine just say ‘pass’
Questions

1. What made you take part in this TC programme?

2. Can you describe your experience of using TrueColours?

3. Can you describe any features that you liked about using TrueColours?

4. Can you describe any features that you didn’t like about using TrueColours?

5. Thinking about the features you liked less, what could we do to make the TrueColours system better?

6. What are the benefits or problems with using it on a regular basis?

7. How has the TC programme impacted on your care?

8. We used a colour coded system to graph your symptoms – green, amber and red. Do you feel that these colours accurately reflected how you felt?

9. You have been answering daily prompts for this six month pilot. Can you tell me how it made you feel to do this? What frequency of email prompts would you have preferred?

10. One of the aims of a technology such as this is to make a people feel more in control of their disease. What are your thoughts about this? How much do you feel that TC has helped you manage your disease?

11. How would you feel about using TC as part of your ongoing care?

12. Is there anything else you would like to add?
Patient Information Leaflet Qualitative Interview at 6 Months

TrueColours Ulcerative Colitis: A pilot study examining real time data collection in patients with ulcerative colitis

You have taken part in the TrueColours programme with your recruitment being approximately 6 months ago. As the study has proceeded it has become obvious that we could get valuable feedback from the participants and therefore you have been invited to talk to Dr Walsh as your feedback is very important to us.

What is the purpose this interview?
One of the aims of this study is obtain feedback about the programme. There are no right or wrong answers to any of the questions. It is your opinions that we are interested in. This will enable us to determine both good and bad aspects of the programme with the aim of improving the programme for the future.

Why have I been invited?
We have selected a variety of participants on the TrueColours programme to ensure that we get feedback from a wide range of participants.

Do I have to take part?
No. Participation is entirely voluntary. If you do decide to participate you can withdraw from the interview at any stage without giving any reason. Withdrawal from this interview will not affect your clinical care.
What will happen to me if I decide to take part?
If you decide to take part in the interview, this will take approximately 30 minutes of your time however this will depend on how much feedback to have to offer. Dr Walsh is willing to spend as much time with you as is needed. The interview will be recorded.

What will happen to the recorded interview?
After the interview has finished, the recording will be transferred to a secure NHS computer. The interview will then be deleted from the recorder. Your TrueColours number will be used to identify the file. The file will then be passed to a professional transcriber. The transcribed file will be returned to Dr Walsh (as a written document). The transcribed version will then be re-read by Dr Walsh to ensure that it is accurate. The transcribed version will be kept (identified only by your TrueColours number and not your name) on a specified file on the NHS server for a period of 3 years at which stage it will be destroyed.

Are there any possible disadvantages or risks from taking part?
This interview will take approximately 30 minutes of your time.

What are the possible benefits of taking part?
This interview will allow you to give us valuable feedback on TrueColours Ulcerative Colitis which we hope will lead to further improvements however it is unlikely that you will get any direct bene

Will my taking part in the study be kept confidential?
Your information will be kept entirely confidential.

Will I be reimbursed for taking part?
There is no financial benefit from participating in this interview. If the interview appointments do not align with your clinical visits (that is, if this requires an extra visit to the hospital), your travel costs will be reimbursed upon issue of valid receipts.

What happens at the end of the interview?
A report or publication will be placed in the public domain at the completion of the study. These results will include information from the qualitative interviews. These results may also be presented at both national and international conferences. You will not be identifiable in any of these reports or presentations. A report will be generated at the completion of the study and will be distributed to all participants.

For additional information now or at any future time please contact:

Dr Alissa Walsh and Professor Simon Travis
Gastroenterology Unit
John Radcliffe Hospital
Headley Way
Oxford
OX3 9DU
Telephone No: 01865 228753
Email: tcuc@ndm.ox.ac.uk
## Appendix M

### Data saturation table for qualitative TrueColours UC interviews

| Themes | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 | 21 | 22 | 23 | 24 | 25 | 26 |
|--------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Usability |   |   |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 1. Acceptability | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 2. Data security | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 3. Reliability | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 4. Usability | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 5. Positive comments regarding email prompts | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 6. Negative comments regarding email prompts | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 7. Usability | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 8. Negative comments regarding interpretation | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 9. Positive comments regarding interpretation | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 10. Usability | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 11. Positive comments regarding interpretation | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 12. Negative comments regarding interpretation | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
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| 15. Usability | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
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| 17. Usability | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
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| 19. Usability | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| 20. Positive comments regarding interpretation | N |  |   |   |   |   |   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

**Notes:**
- N: Not mentioned

**continued...**
Appendix N

Full statistical summary of simulated response for interval k=3

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k = simulated interval between prompt messages being sent, patient = patients are randomly numbered and there is no correlation to their TrueColours UC number, count = number of random simulations, mean = average loss, std = standard deviation, min= minimum value, 25% = first quartile (Q1), 50% = median, 75% = third quartile (Q3), n = number of critical points (SCCAI ≥5) during 6 month pilot
### Full statistical summary of simulated response for interval k=5

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k = simulated interval between prompt messages being sent, patient = patients are randomly numbered and there is no correlation to their TrueColours UC number, count = number of random simulations, mean = average loss, std = standard deviation, min= minimum value, 25% = first quartile (Q1), 50% = median, 75% = third quartile (Q3), n = number of critical points (SCCAI ≥5) during 6 month pilot
Full statistical summary of simulated response for interval $k=7$

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$k$ = simulated interval between prompt messages being sent, patient = patients are randomly numbered and there is no correlation to their TrueColours UC number, count = number of random simulations, mean = average loss, std = standard deviation, min= minimum value, 25% = first quartile (Q1), 50% = median, 75% = third quartile (Q3), n = number of critical points (SCCAI ≥5) during 6 month pilot
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k = simulated interval between prompt messages being sent, patient = patients are randomly numbered and there is no correlation to their TrueColours UC number, count = number of random simulations, mean = average loss, std = standard deviation, min = minimum value, 25% = first quartile (Q1), 50% = median, 75% = third quartile (Q3), n = number of critical points (SCCAI ≥5) during 6 month pilot
## Appendix O

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