Vitamin D supplementation in patients with Crohn's Disease and vitamin D deficiency: D-CODE Feasibility Study

An open label feasibility study for a randomised

controlled trial

by

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Abstract

Introduction: Crohn's Disease (CD) is one form of Inflammatory Bowel Disease (IBD) characterised by severe diarrhoea, abdominal pain, and nutritional problems. Vitamin D deficiency (25(OH)D<50nmol/L) is prevalent in CD, posing the risk of bone disease such as osteoporosis. However, studies suggest that vitamin D deficiency may also impact the symptoms of CD, and lead to poor health-related quality of life. Thus, detecting, treating, and preventing vitamin D deficiency in CD may improve patient outcomes. Nevertheless, current UK national guidance regarding the management of CD does not refer to vitamin D in this high-risk group.

Methods: The method of investigation comprised three different studies: A, B and C.

A – A web-based quantitative/qualitative survey investigating current clinical practice in vitamin D screening and treatment in CD, was distributed to members of the British Society of Gastroenterology IBD section. The survey was open for one month. Survey data was collected using the REDCap online tool.

B – An observational, vitamin D screening study was carried out in the gastroenterology and infusion outpatient departments at the Queen Elizabeth Hospital Birmingham (QEHB). Vitamin D levels were measured by dried blood spot sample. Data regarding modifiable risk factors for vitamin D deficiency were collected including intake of vitamin D-containing foods, smoking and, sun exposure habits.

C – The D-CODE feasibility study for an open label randomised controlled trial (RCT) determining the impact of vitamin D supplementation on health-related quality of life in CD was carried out at QEHB. Only participants identified from study B with identified vitamin D deficiency were recruited. Participants were randomised on a 1:1

ratio to vitamin D supplementation Arm A (400IU cholecalciferol daily for 24 weeks) or Arm B (3,200IU cholecalciferol daily for 12 weeks, followed by 800IU daily for 12 weeks). Patient-reported outcome measures included the IBDQ-32 and EQ-5D-5L.

Results:

A – In total 62 respondents completed the survey. Vitamin D screening was most likely to be carried out annually and in those with small bowel CD or surgery related to their CD. Treatments for vitamin D deficiency included increasing sunlight exposure, dietary changes, and supplementation. However, respondents reported a need for better evidence and national guidance in managing this group.

B – In total 150 patients participated, 53.3% female, mean age 42.7 (SD16.7), ethnicity of participants was predominately white British (77.3%). Prevalence of vitamin D deficiency (25(OH)D <50nmolL) was 53.3%, with CD patients unlikely to improve vitamin D status by alterations in diet or sun exposure.

C – In total 24 patients were consented and 22 randomised. Males and females were evenly matched in both arms, with mean ages 37 (SD15.1) and 38.2 (SD17.5) respectively. Vitamin D levels increased in both arms but was more rapid in Arm B with normal levels achieved by week 12. There were no serious adverse events and doses of vitamin D supplements were safe in the context of this study. The study is feasible with modifications as a future RCT.

Conclusion: This thesis follows a logical pathway in establishing current practice, adding to the body of evidence on the prevalence of vitamin D deficiency, and confirming the feasibility of a future RCT to provide high-grade evidence for clinical management in CD.

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Abbreviations

$1,25(OH)_2D$	1, 25 dihydroxy vitamin D (renal metabolite and biologically active form of vitamin D)
25D	25 hydroxyvitamin D (inactive form of vitamin D)
24,25D	24,25 dihydroxy vitamin D
AE	Adverse Event
CD	Crohn's Disease
CRF	Case Report Form
CTIMP	Clinical Trial of an Investigational Medicinal Product
CTU	Clinical Trials Unit
HRA	Health Research Authority
IBD	Inflammatory Bowel Disease
IDSMC	Independent Data and Safety and Monitoring Committee
IMP	Investigational Medicinal Product
MHRA	Medicines and Health Care Products Regulatory Agency
PPI	Patient and Public Involvement
PROMS	Patient Reported Outcome Measures
R&D	Research & Development
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
RSI	Reference Safety Information
SAE	Serious Adverse Event
SMPC	Summary of Product Characteristics
TMG	Trial Management Group
TSC	Trial Steering Committee
UC	Ulcerative Colitis
UHBFT	University Hospitals Birmingham NHS Foundation Trust
VDBP	Vitamin D binding protein
VDR	Vitamin D Receptors

Publications

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Presentations

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1 Introduction

1.1 Crohn's Disease

Inflammatory Bowel Diseases (IBD) are chronic, debilitating diseases that cause inflammation and ulceration throughout the gastro-intestinal (GI) tract. IBD is most often categorised in to two principal diseases: Crohn's Disease (CD) and Ulcerative Colitis (UC). Where UC usually only affects the colon, CD may affect the entire GI tract from mouth to anus. CD is often diagnosed at an early age but can affect all ages with people presenting to healthcare services with symptoms of severe diarrhoea, abdominal pain, fatigue, and weight loss (2014). Other effects of the disease include iron deficiency anaemia and patients may develop skin lesions, abscesses, or enteric fistulas (Torres et al., 2017). CD activity is characterized by a 'flare and relapse' pattern with periods of remission followed by recurrence of the disease (Kalla et al., 2014, Torres et al., 2017).

CD may be patchy throughout the GI tract, but the terminal ileum is commonly affected (Xavier and Podolsky, 2007). Disease located at the terminal ileum may be particularly problematic from a nutritional aspect, leading to reduced absorption of vitamin B_{12} and bile salts. Bile salts are essential in the digestion and absorption of fats and fat-soluble vitamins; with bile salt malabsorption being an attributing factor to diarrhoea (Nyhlin et al., 1994) and malnutrition in people with CD. A further key feature of the disease is nocturnal defaecation, which sets CD apart from other bowel disorders such as irritable bowel syndrome.

1.1.1 Incidence and prevalence of Crohn's Disease

A recent systematic review suggested that the incidence of IBD generally is increasing across the globe (Molodecky et al., 2012). For CD specifically, the review found that incidence was highest in westernised countries, with the highest reported rates in the United Kingdom (UK) (10.6 per 100,000 person years), Canada (20.2 per 100,000 person years), and Australia (29.3 per 100,000 person years) (Molodecky et al., 2012). Although reported incidence is lower in the east, a recent cohort study involving 181 patients with CD carried out in Asia suggested that the course of the disease in terms of severity, complications, and treatments, is like that reported in Australia. The authors suggest, then, that healthcare practices and costs related to the management of CD will be similar internationally (Ng et al., 2016). A later systematic review of 119 incidence and 69 prevalence population studies reported highest prevalence of CD being in North America (319 per 100,000 persons in Canada) and Europe (322 per 100,000 persons in Germany)(Ng et al., 2017).

In terms of ethnicity CD, and IBD generally, predominates in White populations. However, more recent studies have reported an increasing incidence of CD and IBD in non-White populations. In a large United States of America (USA) population-based study, carried out over 40 years, Aniwan et al., (2019) reported IBD annual incidence in the White population of 21.6 cases per 100,000 person-years (95% confidence interval (CI), 20.0–23.1) and in the non-White population of 13 per 100,000 (95% CI, 8.3–17.5). This showed that IBD was still predominant in the White population, however, the 40-year increase in incidence was 39% in the White population and 134% in the non-White population. This suggests that IBD incidence is increasing more rapidly in non-White groups, although there is a general increase

in all groups. Studies have suggested differences in the clinical manifestation of CD in different ethnic groups. In USA studies, African Americans and those from South Asian backgrounds were most likely to have perianal and fistulating CD, where those from a White background were more likely to have isolated ileal disease (Barnes et al., 2021a). Understanding these trends is important in informing prognosis and future management of the disease.

1.1.2 Aetiology of Crohn's Disease

The aetiology of CD is thought to be immunological in nature, but it is not fully understood. The immunology of the disease can be described on a basic level as an imbalance between T cells that are both pro-inflammatory (T_H17) and regulatory (T_{REG}) (Hansen et al., 2010). In particular, Th1 cells have been identified as key drivers of CD pathology. These cells cause excess production of tumour necrosis factor-alpha (TNF-a), and interferon-gamma (IFN-g) that go on to induce the inflammation and tissue damage characteristic of the disease (Fu et al., 2020).

There is a strong familial link with Saberzadeh-Ardestani et al., (2022) reporting first-degree relatives of patients with CD having a seven-fold increase in the likelihood of developing the disease, in 1438 CD patients studied on the Iranian Registry of Crohn’s and Colitis. A larger population-based study carried out in South Korea (CD n = 17848), showed a 22-fold increase in the risk of CD in first degree relatives (Kim et al., 2021). Generally, both sexes were affected equally in this study. Several genetic factors have been implicated in the development of CD. Identified genes include NOD2, IBD5, IL23R and ATG167L1 (Xavier and Podolsky, 2007, Bairead et al., 2003) with, for example, defective NOD2 leading to impaired bacterial clearance,

suppression of the transcription of anti-inflammatory cytokines and increased inflammation (Xavier and Podolsky, 2007). NOD2 is an intracellular pattern recognition receptor that recognises and responds to bacterial peptides, as part of bacterial surveillance within the innate immune system (Xavier and Podolsky, 2007). Such genetic susceptibility highlights the importance of innate immunity in the pathogenesis of CD (Ogura et al., 2001, Kufer et al., 2006).

Early microbial colonisation of the intestine is essential to the development of a mature immune system (Maynard et al., 2012). Changes or disturbance in intestinal bacteria have been identified as a factor in immune dysfunction in the bowel and the subsequent development of IBD. Van Lierop et al., (2009) describe how commensal bacteria in the intestine can cause an immune response via genetic signalling. Innate cells produce cytokines to attract other immune cells such as neutrophils and macrophages and T and B cells are activated. However, the exact mechanism of microbial dysbiosis is still debated (Rescigno and Nieuwenhuis, 2007). In a previous review of the immune pathogenesis of IBD, de Souza and Fiocchi (2015) identified increased use of antibiotics, western diet, smoking and vitamin D deficiency as key modifying factors for IBD.

1.1.2.1 Antibiotic use

Childhood use of antibiotics has been shown to be a risk factor for developing CD due to the adverse effect of antibiotics on the development of normal microbiota (De Souza and Fiocchi, 2015). A Danish cohort study involving 577 627 children born between 1995 and 2003 showed that those who had received antibiotics were 3.41 times more likely to be diagnosed with CD (18% increase in the risk of CD for each

course received) (Hviid et al., 2011). They found that there was no similar increase in risk for UC and that CD risk was greatest in the first 3 months following a course of antibiotics (RR 4.43) and among children who had received ≥7 courses of antibiotics the risk was greater still (RR 7.32).

A British study found similar effects in an adult population (Card et al., 2004). A total of 587 CD cases and 1460 controls were analysed from the General Practitioner Research Database. Antibiotic use 2 to 5 years prior to CD diagnosis occurred in 71% of cases compared to 58% of controls ($p<0.001$). The median number of courses of antibiotics was one in the controls and two in the cases ($p<0.001$). Adjusting for use of other medicines, age, sex and smoking; antibiotic use had an odds ratio of 1.32 (1.05–1.65) suggesting an associative link (Card et al., 2004). Furthermore, a systematic review published in 2018 suggested a positive correlation with antibiotic use and the risk of developing CD particularly in those with a genetic susceptibility (Theochari et al., 2018).

1.1.2.2 Western diet

The western diet is classified by high saturated fat and sugar intake and a low fibre intake. This type of diet has been shown to alter the intestinal microbiota (Statovci et al., 2017), increase intestinal permeability and promote inflammation (Uranga et al., 2016). Explanations for this include animal-based fats and proteins causing dysbiosis in the gut microbiota leading to a low grade, chronic inflammatory response (Reddavide et al., 2018). However, evidence for this is inconclusive. In a prospective study of participants from the Nurses' Health Study (n = 170,805) dietary intake of saturated fat was associated with the risk of UC but not CD (Ananthakrishnan et al.,

2014). However, a multi-centre case control study of IBD patients in Japan (CD 160, UC 131, Controls 273) found that higher risk of CD was associated with sugar/sweetener intake 2.12 (95% CI, 1.08 to 4.17), sweets 2.83 (95% CI, 1.38 to 5.83), and fats and oils 2.64 (95% CI, 1.29 to 5.39). Interestingly, there was also an increased risk with fish and shellfish intake 2.41 (95% CI, 1.18 to 4.89) (Sakamoto et al., 2005). Conversely, a case control study in 332 children (130 CD, 202 controls) explored protective dietary factors and found that consumption of fish (OR 0.46, 95% CI 0.20-1.06, P= 0.02), vegetables (OR 0.69, 95% CI 0.33-1.44, P= 0.03), fruits (OR 0.49, 95% CI 0.25-0.96, P= 0.02) and dietary fibre (OR 0.12, 95% CI 0.04-0.37, P < 0.001) reduced the risk of CD (Amre et al., 2007).

1.1.2.3 Smoking

Smoking is suggested to be an independent risk factor for CD (Parkes et al., 2014). A meta-analysis identified nine studies regarding risk of CD secondary to smoking. Two of the included studies showed no relationship where the remaining studies showed an increased risk (95% CI, 1.40-2.22; P<.001) (Mahid et al., 2006). The reasons for this correlation are unclear. It has been hypothesised that smoking may affect the intestinal microbiota or that smokers may have other lifestyle factors that lead to increased risk (Parkes et al., 2014).

1.1.2.4 Vitamin D deficiency

Vitamin D deficiency broadly refers an insufficient quantity of vitamin D in the body to carry out necessary functions and maintain health. Bone health is often the key clinical marker of vitamin D status due to the well-recognised role vitamin D plays in calcium homeostasis. However, there are vitamin D receptors (VDR) in many cells throughout the body**.** Active vitamin D 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) binds

to the VDR and together with other transcription factors, regulates gene transcription in those cells (Cantorna, 2006, Carlberg, 2018, Nurminen et al., 2019). Vitamin D is recognised as a modulator of the immune system (Morán-Auth et al., 2013, Ismailova and White, 2022). Studies have shown that vitamin D deficiency accelerates the development of auto-immune diseases such as IBD in mouse models (Froicu et al., 2003, Liu et al., 2008, Lagishetty et al., 2010). In patients with diagnosed disease, vitamin D deficiency has been shown to correlate with increased CD activity (López-Muñoz et al., 2019, Hausmann et al., 2019). Although CD causation is likely to be multi-factorial, evidence suggests that vitamin D status plays a pivotal role in both the development and management of the disease. This facet of vitamin D is the focus of the current thesis and will be discussed in greater detail in subsequent sections

1.1.3 Management of Crohn's Disease

CD is an incurable disease. Although elective surgery may be an option where CD is limited to the distal ileum or colon, in stricturing CD or in those with refractory disease (National Institute for Health and Clinical Excellence [NICE], 2019, Lightner et al., 2020, Butt et al., 2020), the risk of post-operative complication is high. Post-operative complications include intra-abdominal sepsis and anastomotic leaks (Shah et al., 2021). Patients who are poorly nourished have been shown to have the highest post-operative risks (Reindl et al., 2019, Yamamoto et al., 2020). Hence careful consideration should be given to the patient's history, nutritional status and previous medication use prior to surgical intervention to ensure all non-surgical management options have been explored (Bemelman et al., 2017).

Medical management of CD is usually centred on controlling symptoms and inducing remission by dampening the inflammatory action of the disease. NICE CD guidance

(2019) details several recommended medication regimens to achieve this. Treatments to inhibit inflammation include the use of glucocorticoid steroids (for example prednisolone), amino-salicylates (also known as 5-ASAs, for example sulfasalazine), immunosuppressants (for example methotrexate and azathioprine) and anti-tumour necrosis factor α (TNFα) antibody therapy (for example infliximab and adalimumab). Although effective at inducing remission, preventing hospitalisation (Mao et al., 2017) and promoting mucosal healing (Ungaro et al., 2020), these medications may have severe side-effects.

Prolonged use of glucocorticoid steroids reduces bone density leading to the development of osteoporosis in adults (Moghadam-Kia and Werth, 2010) and stunted growth in children (Mushtaq and Ahmed, 2002). NICE CD guidance recognises CD as a cause of osteoporosis (Tan et al., 2014, Lima et al., 2017, Soare et al., 2021) and suggests further reference to NICE osteoporosis guidelines (2017) to identify those at risk of osteoporotic fracture. Despite this, the significant role that vitamin D plays in the musculoskeletal health of patients with CD is not covered in national guidance.

Blocking the ability of the inflammatory cytokine TNFα successfully restricts inflammation but may also impeded other functionally important immune responses. Anti-TNFα and immunosuppressant therapy may lead to an increased risk of serious infections (Blanchard et al., 2017, Singh et al., 2020), development of some cancers (Shivaji et al., 2019) and reactivation of tuberculosis with anti-TNFα treatments particularly (Keane et al., 2001). Despite this the use of anti-TNFα demonstrated remission within 4 weeks of treatment in trials (Hanauer et al., 2006) and provides a

rapid and sustained clinical remission that has been unachievable with other treatments (Adegbola et al., 2018).

1.1.4 COVID-19 Pandemic and CD

COVID-19, caused by novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a virus identified as the cause of an outbreak of respiratory illness first detected in Wuhan, China in 2019. A global pandemic of the disease rapidly developed resulting in 557,917,904 confirmed cases and 6,358,899 deaths worldwide by 15th July 2022 (World Health Organisation, 2020). During March 2020, the UK government implemented a national 'lockdown' to manage the spread of the virus across the country. This led to changes in the management and delivery of research and healthcare to reduce the risk to participants and members of the public, and to protect the National Health Service (NHS). In anticipation of unprecedented pressures caused by the pandemic, the NHS cancelled all elective surgery (Iacobucci, 2020), non-urgent outpatient appointments were cancelled or converted to telephone consultation only, and clinical staff from all specialities were redeployed to areas of highest need (Oliver, 2020).

A study in the USA reported prevalence of COVID-19 infection among people with IBD as 3% (5/168) at the start of the pandemic (Gubatan et al., 2020). An Italian study at a similar time recorded no cases of COVID-19 among people with IBD (Norsa et al., 2020). The British Society of Gastroenterology (BSG) reported early COVID-19 prevalence from the international Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE)-IBD Registry. At the time of publication there were 239 internationally reported cases of COVID-19 in IBD patients on the registry (137 CD, 94 UC, 5 IBD unclassified) (Kennedy et al., 2020). Kennedy et al (2020) report

that of these 64 were hospitalised and 11 patients died. In 2021, a systematic review of 24 COVID-19 studies from across the world in people with IBD found that incidence of COVID-19 per 1000 patients was lower than in the general population at 4.02 (95% confidence interval (CI, 1.44–11.17) in IBD and 6.59 (3.25–13.35) in the general population. There was no increase in relative risk (0.47, 0.18–1.26) in IBD (Singh et al., 2021).

A prospective observational study of 6273 patients with CD had previously shown that active disease (HR=2.24, 95% CI=1.57, 3.19; *P*<0.001), use of prednisolone (steroid therapy) (HR=1.57, 95% CI=1.17, 2.10; *P*=0.002), and infliximab (biologic treatment) (HR=1.43, 95% CI=1.11, 1.84; *P*=0.006) were independently associated with the risk of serious infections (Lichtenstein et al., 2012). The most common serious infection was pneumonia with an incidence 0.17/100 patient-years of follow-up. While the risk that COVID-19 posed to people with IBD was unknown and prevalence was low, the BSG quickly issued advice on the management of patients with IBD during the pandemic. Management measures were stratified in to three categories depending on co-morbidities and IBD related treatment. These were shielding, stringent social distancing and social distancing. Patients were advised to continue their current IBD medications but with some treatments, such as biologics, being stopped if they developed any COVID-19 symptoms. In terms of clinical services, the BSG recommended that:

- Outpatient appointments should be conducted via telephone/video to reduce face to face contact.
- Access to injectable treatment should be maintained, irrespective of risk category and social distancing/isolation recommendations.

- Infusion suite services should be maintained as a priority area to prevent treatment flare and hospital admission (Kennedy et al., 2020).

Of interest, amid the treatments developed for the management of COVID-19 in the last couple of years, vitamin D status has been highlighted as an influencing factor on outcome from COVID-19 infection (Martineau and Cantorna, 2022). Where vitamin D supplementation has been shown to reduce acute respiratory infections generally (Martineau et al., 2017), evidence for vitamin D in the management of COVID-19 is inconclusive to date (Farid et al., 2021, Martineau and Cantorna, 2022).

1.2 Vitamin D

1.2.1 Discovery of Vitamin D

Vitamin D is one of four fat-soluble vitamins, meaning that it has a cholesterol like hydrophobic structure that results in it being absorbed in fat and stored in fat within the body. Fat-soluble vitamins were discovered in the early twentieth century when scientists recognised an ‘indispensable organic complex’ within some foods, such as butter and eggs, that were essential for normal growth and reproduction. The first of these is now known as vitamin A (Mccollum and Davis, 1913). Following this earlier discovery, Sir Edward Mellanby hypothesised that rickets could be caused by a similar nutritional or vitamin deficiency. In his work, he found that cod liver oil was a cure for rickets in rachitic dogs (Mellanby, 1919). Shortly after, McCollum et al (1922) discovered an active ingredient within cod liver oil that was responsible for calcium deposition, and this ingredient was identified as vitamin D.

Around the same time, experiments into the development of rickets in Austrian children discovered the impact of sunlight exposure on the disease. Restricted diets

were given to young children to see which diet was most likely to induce rickets. None of the children developed rickets during the summer months but many children, given one type of diet, developed rickets during the winter. Hence, it was determined that, in addition to diet, sunlight exposure had a major influence on vitamin D status and the subsequent development of rickets (Chick et al., 1923).

1.2.2 Role of Vitamin D in Musculoskeletal Health

A key function of vitamin D is its role in increasing calcium absorption from the intestine, calcium that may then be used for bone deposition. The active form of vitamin D 1,25(OH)2D, also known as Calcitriol, binds to VDR in the cells of the intestinal lining (enterocytes). Through genomic action the cell produces more calcium transporters to increase the amount of calcium that is taken into the enterocyte; and to increase the action of the calcium pump in moving calcium out of the cell and into the blood stream (Christakos et al., 2011). In the absence of adequate vitamin D or calcium intake, parathyroid hormone stimulates the release of calcium stored in bone to maintain serum levels of calcium (Christakos et al., 2011). Clinical trials have gone on to confirm this role and the important function of vitamin D in fracture prevention (Bischoff-Ferrari et al., 2009) and muscle strength (Beaudart et al., 2014).

Common signs and symptoms of vitamin D deficiency include bone deformity and disease such as rickets (Uush, 2013) and osteomalacia (Minisola et al., 2021), hypocalcaemia sometimes leading to death in infants and young children due to cardiac muscle dysfunction (Basatemur and Sutcliffe, 2015), musculoskeletal weakness and musculoskeletal pain in adults (Gokcek and Kaydu, 2018).

1.2.3 Role of Vitamin D in Crohn's Disease

In our recently published review, we explored the mechanistic basis for a role for vitamin D in CD and IBD (Fletcher et al., 2019). The immuno-modulatory properties of 1,25$(OH)_2$D include anti-inflammatory (Cantorna, 2012, Adams and Hewison, 2008) and antibacterial (Liu et al., 2006, Bacchetta et al., 2014, Hewison, 2011) actions on the cells of the innate and adaptive immune systems. These immune systems modulate the pathology of gastrointestinal inflammation and dysregulation. Vitamin D is also important in the integrity and maintenance of the gastrointestinal barrier by regulating proteins associated with epithelial cell gap junctions (Zhang et al., 2015, Liu et al., 2013, Kong et al., 2008). Furthermore, the barrier function of vitamin D is associated with its impact on the gastrointestinal microbiota. Vitamin D status in humans is correlated with changes in gastrointestinal bacteria associated with inflammatory immune responses (Luthold et al., 2017, Garg et al., 2018). Therefore, it has been suggested that vitamin D has the potential to ameliorate disease activity through anti-inflammatory immune responses, and through its effects on barrier function and microbiota homeostasis (Fletcher et al., 2019).

Patients with active CD often report having a poor health related quality of life because of their disease (Casellas et al., 2001, Hlavaty et al., 2014) and vitamin D deficiency is associated with severity of CD (Lu et al., 2015). Studies have suggested that supplementing vitamin D in these patients reduces disease inflammatory markers such as TNF-α (Dadaei et al., 2015). However, other cohort studies have been less conclusive. Jun et al (2019), found a correlation between C-reactive Protein (CRP) and serum vitamin D in patients with CD, but supplementation did not improve the CRP levels. A large retrospective, cohort study of 3217 patients with IBD, 55% of

which had CD, found that 17% of CD patients with vitamin D deficiency required surgery or hospital admission compared to just 10% in the group with normal levels (Ananthakrishnan et al., 2013). Subsequent normalisation of vitamin D levels showed a reduced risk for patients needing CD related surgery or hospitalisation (OR 0.56, 95% CI 0.32 – 0.98) (Ananthakrishnan et al., 2013). Other studies have suggested that vitamin D may work in cooperation with CD treatments such as Infliximab to reduce inflammation (Stio et al., 2004, Reich et al., 2014).

Vitamin D deficiency may also have an impact on the development of anaemia in patients with CD. Anaemia is prevalent in patients with chronic inflammatory processes such as CD, with anaemia of chronic disease found in between 43%-63% of patients with IBD (Bergamaschi et al., 2010, Fialho et al., 2015). The mechanism for this is believed to relate to how the hormone hepcidin is released in the intestine. Hepcidin is the main hormone that controls iron absorption from food in the intestine. When iron stores are replete in the body, hepcidin reduces the intestine's ability to absorb iron. When iron stores are deficient, less hepcidin is released which allows the intestine to absorb more iron. However, it is recognized that the chronic inflammatory process causes excess production of hepcidin which leads to poor iron absorption even when the body is deficient (Sun et al., 2012). This then contributes to the development of iron deficiency anaemia (Sun et al., 2012). This effect has been shown specifically in patients with CD as a cause of anaemia (Basseri et al., 2013).

Recent studies have suggested a role for vitamin D supplementation in reducing over-production of hepcidin (Zughaier et al., 2014, Bacchetta et al., 2014). The mechanism of this is thought to be by direct suppression of hepcidin gene expression (Zughaier et al., 2014). The study by Bacchetta et al (2014) in healthy volunteers

given a single dose of vitamin D supplement (100,000IU), showed that this reduced hepcidin levels by 34% within 24 hours. In other patients with anaemia of chronic disease, such as those with chronic kidney disease (CKD), vitamin D supplementation has been shown to cause a reduction in hepcidin levels (Zughaier et al., 2014). In a placebo-controlled pilot study of 38 patients with CKD, high dose (50,000IU) Cholecalciferol was given weekly for 12 weeks and then alternate weeks for a year. The results showed a reduction of hepcidin in response to increased blood concentration of 25(OH)D (Zughaier et al., 2014).

Though these studies suggest a positive effect from vitamin D on the activity and effects of CD, there are few randomised controlled trials (RCTs) investigating the general extra-skeletal effects of vitamin D supplementation (Rejnmark et al., 2017). In terms of CD and IBD specifically, evidence for vitamin D supplementation is mostly observational in nature with some RCT's giving conflicting evidence (Nielsen et al., 2019) (see section 4.2).

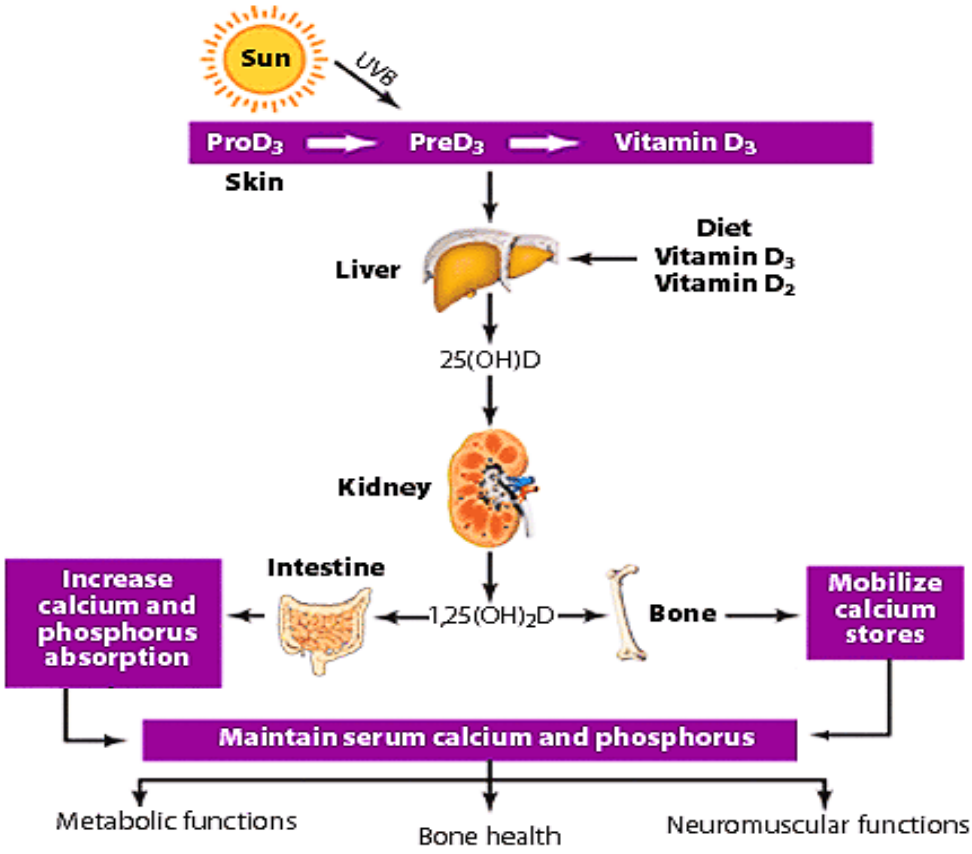
1.2.4 Sources of Vitamin D

Primary sources of vitamin D include synthesis from sunlight exposure, diet/food sources and dietary supplementation, either prescribed or over-the-counter.

1.2.4.1 Sunlight Exposure

In humans the main source of vitamin D is via synthesis in the body stimulated following epidermal exposure to ultraviolet B-light (UVB) (Reich et al., 2014). Figure 1-1 shows the process of vitamin D synthesis. The liver produces the vitamin D precursor, 7-dehydrocholesterol (also known as pro-vitamin D3), which is stored in the skin. On exposure of the skin to UVB light, this is converted to pre-vitamin D3,

and then to vitamin D3, before entering the blood stream. In the liver vitamin D3 is converted to the inactive form of vitamin D, $25(OH)D_3$. Further, conversion by the kidneys of $25(OH)D_3$ produces the active form of vitamin D $1,25(OH)_2D_3$ (Reich et al., 2014). Although D3 forms of 25(OH)D and $1,25(OH)_2D$ predominate in the circulation, D2 forms of 25(OH)D and $1,25(OH)_2D$ can also be formed from ergocalciferol; which is found in some plants, mushrooms, and supplements.



(Duarte, 2015)

Figure 1-1: Synthesis of vitamin D from UVB light and diet

The Scientific Advisory Committee on Nutrition (SACN) (2016) note that lack of adequate exposure to sunlight is likely to lead to vitamin D deficiency, defined by

SACN as serum levels of 25(OH)D <25 nmol/L. However, it is difficult to determine what constitutes adequate exposure. In their study, Rhodes et al (2010) found that the time required to synthesise vitamin D is usually short and generally before skin begins to burn or redden. They determined that, in light-skinned people, sunlight exposure for an equivalent of 13 minutes of UK (approximate latitude 53.4808° N, 2.2426° W), summer midday sun three times each week during a six-week period was sufficient to increase vitamin D levels above 50 nmol/L. Participants wore no sunscreen and had one third of their skin exposed to simulated UVB light (Rhodes et al., 2010). The study found that participants with darker skin required a longer exposure to simulated sunlight to produce vitamin D. Furthermore, Rhodes et al (2010) note that excessive cutaneous exposure to sunlight may in fact lead to degradation of vitamin D but they do not quantify what excessive exposure is (Rhodes et al., 2010).

A recent global consensus statement on the treatment and prevention of rickets noted that there is no safe threshold of sunlight exposure that allows for adequate vitamin D synthesis without increasing the risk of skin cancer (Munns et al., 2016). The authors suggest that the use of sunlight exposure to prevent or treat rickets or vitamin D deficiency is not feasible (Munns et al., 2016). The issue of sunlight exposure is of particular importance to patients with IBD, where there is an increased risk of non-melanoma skin cancer in those who have received thiopurines as a treatment for IBD (Magro et al., 2014, Huang et al., 2019, Setshedi et al., 2012). Patients with CD and other forms of IBD may be advised to avoid sun exposure when they are receiving this type of immuno-suppressant therapy for their disease (Fletcher, 2016).

1.2.4.2 Dietary Sources of Vitamin D

The majority of vitamin D, as vitamin D3, naturally occurring in food is found in animal-based products (Schmid and Walther, 2013). The quantity of vitamin D found in animal products may vary according to the vitamin D status of the animal. As in humans this will be influenced by the animal's exposure to sunlight, their diet and if they receive vitamin D supplementation in their feed (Roseland et al., 2018). The addition of vitamin D to livestock feed in the USA has been shown to improve the quality of the meat by increasing tenderness (Carnagey et al., 2008) but this is not a universal practice. Different forms of vitamin D are found in different types of animal products. For example, in dairy products vitamin D2 is found but in meat products the more potent vitamin D3 (see 1.2.6) is found (Schmid and Walther, 2013). There is a continued emphasis on animal sources of vitamin D. However, Black et al (2017), stress the importance of further research into plant-based foods in providing vitamin D in the diet. This is particularly important when considering the intake of food and dietary supplements in people who observe vegetarian or vegan diets.

In the update of their report, SACN (2016) confirmed that the recommended daily intake for vitamin D from all sources including both diet and oral supplementation, is 10µ (400IU) per day for those aged 4 years and over. It is estimated that this is enough to maintain vitamin D 25(OH)D levels >25nmol/l. However, maintaining this intake from food sources alone is difficult in the UK diet. There are few foods that contain significant quantities of vitamin D. Therefore, the majority of intake in the UK is from regular consumption of foods containing lesser amounts of vitamin D.

NHS Choices (2017) recommend the following food sources of vitamin D:

- oily fish – such as herring, salmon, sardines, and mackerel
- egg yolks
- red meat
- liver
- fortified foods – such as some fat spreads and breakfast cereals

There are notable differences in the amount of vitamin D in each of the foods mentioned. Table 1-1 gives examples of some of these foods and the quantity of vitamin D contained in each.

Table 1-1 Vitamin D Content of Common Foods

Food Stuff*	**Vitamin D content per 100g serving in micrograms µg (range)**
Grilled bloater	25.0
Grilled herring	16.1
Canned salmon, pink	13.6 (3.4 -13.6)
Grilled mackerel	8.5
Grilled sardines	5.1 (3.2-5.1)
Fresh baked tuna	3.1 (1.1 -3.2)
Pork (various)	1 approx.
Beef (various)	< 1
Liver (various)	1 approx.
Boiled egg yolk only	12.6
Boiled whole egg	5.0
Fortified fats	8.4
Fortified breakfast cereal (malted flakes)	8.3

*Data extracted from McCance and Widdowson Composition of Foods Integrated Dataset (Public Health England, 2019a). Where several versions of prepared, raw, or cooked food are given the version with the highest available value is quoted. The values for eggs demonstrate that vitamin D is concentrated within the yolk, rather than whole egg. Note NICE guidance recommends 10µg vitamin D intake per day.

Oily fish is generally a useful source of vitamin D, though there are inter-source variations. Fish such as bloater contain significant quantities of vitamin D (25µ per

serving). However, oily fish may not be commonly consumed as part of a UK diet. Shafique et al (2018) report an analysis of UK Biobank dietary intake data. Of the 164,573 sets of participant data analysed, only 20% reported consuming two portions of oily fish per week. In the UK, adults aged 19-64 years obtain their vitamin D intake from a variety of other foods. The main dietary sources of vitamin D intake are meat (providing 30% of total vitamin D intake), fortified fats (19%), all cereals (13%), eggs and egg dishes (13%), and oily fish (providing 11% of vitamin D intake) (SACN, 2016). Meat contains a relatively small amount of vitamin D and so would need to be consumed in large quantities to achieve a significant intake.

Despite these common dietary sources, vitamin D intake remains below the recommended 10 µg/day (400IU). The UK National Diet and Nutrition Survey (NDNS) (Public Health England, 2017) reported that in adults aged 19-64 years, mean daily intake of vitamin D from dietary sources was just 2.8µg (112 IU). Even when consumption of vitamin D supplements is considered, mean daily intakes only increased to 3.9µg (156 IU) in men and 3.4µg (136 IU) in women. However, the updated NDNS of 2019 (Public Health England, 2019b) found that intake of vitamin D had reduced by 2% in men and 1% in women compared to earlier estimates. This suggests that in the general population, diet with or without self- supplementation is inadequate to maintain even a modest recommended daily intake of vitamin D.

1.2.4.3 Food Fortification Policy

There are ongoing questions regarding the fortification of core foods with vitamin D in the UK to increase intake at a population level (Cribb et al., 2015). In Canada fortification of milk and margarine is mandatory with plans to expand this to other foods (Health Canada, 2019). In the UK in 2017, a Parliamentary question was asked

by Lord Hunt of Kings Heath (Rickets: Written Question HL3098) regarding the government's intention to fortify foods. The Government of the time confirmed that there were no plans to introduce mandatory fortification of foods with vitamin D in the UK (Department of Health, 2017).

1.2.5 Vitamin D Dietary Intake in People with Crohn's Disease

Early RCTs have shown that manipulation of dietary intake in people with CD has positive effects on symptoms and induces remission for longer than traditional corticosteroid treatment (7.5 months vs 3.8 months respectively, p=0.048) (Riordan et al., 1993). This later lead to the development of a Crohn Disease Exclusion Diet (CDED). A CDED is one that excludes foods thought to affect the gut microbiome or gut permeability or one where specific individual food sensitivity is noted. CDED would usually be sustained for a fixed period with reintroduction of normal table foods after this. In one study excluded foods included any containing gluten, gluten-free baked goods and breads, dairy products, animal fat, processed meats, products containing emulsifiers, all packaged products with a due date and tinned goods (Sigall-Boneh et al., 2014). In this cohort study of adults (n = 13) and children aged 4 – 18 years (n = 34), CDED was prescribed for 12 weeks with the aim of inducing remission as reported by a disease index and biochemical markers. Full remission was achieved by week 6 in 70.1% of child participants and 69.2% of adult participants. In the child participants where disease index stratification was reported remission was more frequent in those with mild (75%) or moderate (71%) disease, and less frequent in those with severe disease (33.3%). A recent RCT in 78 children found that CDED used with partial feeding with liquid enteral nutrition, compared to exclusive liquid enteral nutrition, was better tolerated and demonstrated remission at

12 weeks (Levine et al., 2019). A cohort study of 40 adult patients refined the CDED to exclude specifically IgG4 containing foods, which are known to be a dominating food antigen (Rajendran and Kumar, 2008). Participants excluded the four most individual immunoreactive foods from their diet for four weeks. There was a dropout rate of 27% in the study, however, data for the remaining participants showed a significant reduction in disease index score (p=0.0001) and there was a significant reduction in IgG4 seroreactivities at the end of the period (p=0.003). The foods most often excluded for the purposes of the study were eggs, red meat and cheese (Rajendran and Kumar, 2011).

Studies have suggested that people with CD restrict their diet to help manage the symptoms of their disease (Larussa et al., 2019, Bergeron et al., 2018). Belief that certain foods can exacerbate symptoms is more prevalent amongst the Asian-British population than the White-British population (71% versus 47%, p = 0.005) (Limdi et al., 2016). Reported restricted foods are often similar to those described in the CDED. A small cross-sectional study of dietary intake in 31 patients with IBD in Iceland reported that patients avoided processed meat products (55%) and dairy products (60%) due to adverse effects on the symptoms of their IBD. In the same study, some patients (22%) reported that eating fish had a positive effect on their symptoms (Vidarsdottir et al., 2016). A Dutch cross-sectional study of 165 patients with IBD compared to healthy controls, demonstrated that patients with IBD consumed more meat and poultry with an average difference of 15.0g/day (95% CI 8.50-21.4); fewer dairy products (apart from cheese) at -36.3 g/day (95% CI -65.8- -6.84); and slightly less fish at -1.42 g/day (95% CI -0.94- -3.79) (Opstelten et al., 2018).

Vagianos et al (2007) reported dietary and food avoidance data for 319 patients with IBD in the Manitoba IBD Cohort Study in Canada. They found that the foods most avoided, secondary to GI upset, included deep-fried/higher fat foods, red meat, milk products, fruit, vegetables, salad, nuts, and seeds. A recent UK cross-sectional study of 67 patients (CD n = 40, UC n =23, other colitis n = 4) found that food avoidance was seen in 65 (97%) patients (Krishnamoorthy and Jeanes, 2018). The mean number of foods avoided was 6 including vegetables (60%) and wheat-based products (56%). Sixty per cent of respondents reported that food was associated with disease activity. Mean vitamin D intake was estimated to be 282.9IU/day (Krishnamoorthy and Jeanes, 2018).

It is noteworthy that some excluded foods in both the CDED and reported self-restricted diets are those that may be important dietary sources of vitamin D, including eggs, red meat, and fats/dairy products. These small studies suggest that patients with IBD are unlikely to consume adequate amounts of vitamin D rich foods even in a prescribed diet.

1.2.6 Vitamin D Supplementation

Oral supplements containing vitamin D are widely available both as prescription-only medicines and over-the-counter as food supplements. Supplements may be single or multi-nutrient preparations. There are a variety of vitamin D supplements available over-the-counter, with variable combinations, doses, and potency (Leblanc et al., 2013). Vitamin D supplements contain either ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3). Both vitamin D2 and D3 are metabolised by the liver to 25(OH)D. However, studies suggest that vitamin D3 appears to yield more 25(OH)D than an equal amount of vitamin D2, with vitamin D3 being more effective at raising

serum levels (Tripkovic et al., 2012, Glendenning et al., 2013). For this reason, vitamin D3 is usually recommended (Francis et al., 2018, Holick et al., 2011).

Nevertheless, the amount of vitamin D supplementation required to prevent deficiency is an area of debate. The European Food Safety Authority (2012) set an upper tolerable limit for vitamin D supplementation of 4,000IU daily in adults. In accordance with SACN (2016), current NICE (2017) recommendations are 400IU/day vitamin D. The Institute of Medicine (IOM) (Ross et al., 2011) suggest an intake of 600IU/day to maintain a 25(OH)D serum levels of >50 nmol/L, with the Endocrine Society (Holick et al., 2011) recommending intakes for adults of 1500IU–2000IU/day to maintain similar levels. SACN (2016) recognise that the intake level they have set is for population protection from rickets rather than optimal health in individuals.

However, none of these guidelines address the risks for people with inflammatory, malabsorptive diseases such as CD and other forms of IBD. A recent review has suggested that in IBD doses of 1,800IU -10,000IU daily may be required due to malabsorption of nutrients from the intestine (Hlavaty et al., 2015). With such a wide dosing range it is difficult to determine the amount that is likely to be most effective in this patient group (Fletcher et al., 2019). A titrated dosing regimen is generally recommended when using supplements in clinical practice to include a loading dose followed by a maintenance dose (Francis et al., 2018). However, it is important to consider the quality of the vitamin D supplement being used. In an analysis of five pills from each of 15 different bottles of over-the-counter vitamin D supplements, Le Blanc et al., (2013) discovered a wide variation in vitamin D content compared to the stated dose on the label. Comparable results have been found in other studies.

However prescribed vitamin D supplements, the production of which is more tightly regulated, were found to have content values within standard acceptance ranges (Garg et al., 2013) and so are a more reliable method of supplementation.

1.3 Vitamin D Deficiency

1.3.1 Measuring Vitamin D

The measurement of serum total 25(OH)D is recommended as the best estimate of circulating vitamin D levels. Total 25(OH)D is comprised of the 25-hydroxylated forms of both vitamin D2 and D3, 25(OH)D_2 and 25(OH)D_3 (Berry et al., 2017). 25(OH)D and other vitamin D metabolites travel through the circulation bound primarily to vitamin D binding protein (VDBP), although binding to other abundant serum proteins such as albumin is also observed (Chun et al., 2019). VDBP is a multi-functional protein which, in addition to being a carrier of vitamin D metabolites, also functions as a serum actin-binder and macrophage-activating factor (Bikle and Schwartz, 2019). VDBP is also a negative acute-phase protein, meaning that levels of VDBP are lowered in response to conditions such as inflammation, in favour of hepatic production of positive acute-phase proteins such as C-reactive Protein (CRP). Studies have suggested that, in the presence of inflammation, circulating 25(OH)D levels will be reduced due to the lack of carrier VDBP, rather than a true deficiency of vitamin D (Waldron et al., 2013, Reid et al., 2011). In a systematic review of eight longitudinal studies measuring vitamin D and/or VDBP after an acute phase, six demonstrated that 25(OH)D levels were decreased during or shortly after an inflammatory episode (Silva and Furlanetto, 2015). They suggest that vitamin D levels should be interpreted with caution in the presence of inflammation. As CD is characterised by inflammation, there is speculation that low 25(OH)D levels may be

indicative of the reduction in VDBP during inflammation, rather than true deficiency of vitamin D in this patient group.

Aksan et al (2020) studied 188 patients with IBD (CD n=84, UC n=104). Using CRP and faecal calprotectin as markers of inflammation. They compared serum levels of 25(OH)D, VDBP and two other vitamin D metabolites: 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) and 24,25-dihydroxyvitamin D ($24,25(OH)_2D$). The authors report that serum 25(OH)D was the only vitamin D metabolite that showed no correlation with inflammatory markers. Although 1,25D is the active form of vitamin D, it is the inactive form of vitamin D that is more relevant to inflammatory disease. Current data suggest that anti-inflammatory effects involve local tissue-specific conversion of 25D to 1,25D. This is not impacting serum levels of 1,25D. Further research is required to explore this relationship but within clinical practice, serum levels of 25(OH)D continue to be the standard measure of vitamin D status.

1.3.2 Defining Vitamin D Deficiency

There continues to be debate globally regarding the optimal serum level of vitamin D required for health. In the UK, the Rank Forum on Vitamin D (Lanham-New et al., 2011) concluded with agreement that it was desirable for the population to have a serum level of 25(OH)D >25 nmol/L. It was recognised that this was an important 'cut-off' below which the risk of bone disease was increased. However, there was uncertainty regarding the strength of evidence recommending higher concentrations of >50 - 75nmol/L from mostly observational and cohort studies. The forum recognised the need for RCTs to establish the benefit of a higher 'cut off' level. As such the UK recommended level remains >25nmol/L to meet the musculoskeletal needs of 97.5% of the population (SACN, 2016, NICE, 2017).

In contrast, the USA National Academy of Medicine (formerly the Institute of Medicine) (Ross et al., 2011) and the Australian Government (2019) recommend a cut off of >50nmol/L to meet the needs of the population for optimal musculoskeletal health. These are in line with recommendations from osteoporosis specialist groups globally (Nowson et al., 2012, Holick et al., 2011) with the National Osteoporosis Society in the UK issuing pragmatic guidance (Francis et al., 2018) as follows:

- 25(OH)D <25 nmol/L (10ng/ml) is deficient
- 25(OH)D of 25–50 nmol/L (10-20ng/ml) may be inadequate in some people
- 25(OH)D >50 nmol/L (20ng/ml) is sufficient for most of the population

Many studies investigating vitamin D deficiency in IBD often report deficiency as being 25(OH)D levels <50nmol/L. However, a recent review suggested that vitamin D serum levels of >75nmol/L were associated with improved clinical outcomes and inflammatory markers (Nielsen et al., 2018, Nielsen et al., 2019). Although, this higher serum level is in accordance with recommendations from the Endocrine Society of North America (Holick et al., 2011), it cannot be deemed a cut-off point to indicate deficiency in those with CD or IBD specifically. There continues to be no universally agreed optimal serum level of vitamin D in any group.

Nevertheless, vitamin D deficiency is recognised as a major public health concern and indeed is pandemic in Europe (Cashman et al., 2016). In their study of pooled data for 55,844 people across Europe, Cashman et al (2016) found that overall, 13% of the reported population had vitamin D levels <30nmol/L and 40.4% had levels <50nmol/L. A systematic review of globally reported data found that the prevalence of vitamin D deficiency was high across the world in all age groups, even in countries

with a high degree of sun exposure (Palacios and Gonzalez, 2014). The highest reported prevalence was in young women in the middle east with 81% having vitamin D levels <30nmol/L (Palacios and Gonzalez, 2014). This is most likely be due to cultural reasons where women and girls keep their skin covered and so have limited sun exposure to synthesise vitamin D. Clearly results are restricted by the availability of reported data in each country.

In the UK vitamin D deficiency is addressed by NICE in their guidance regarding increasing vitamin D intake in people at the highest risk of deficiency (NICE, 2017). High risk groups are identified by NICE as infants and children aged under four, pregnant and breastfeeding women, particularly teenagers and young women, people aged over 65 years, people who have low or no exposure to the sun and people with darker skin. However, the measurement of vitamin D serum levels is somewhat contentious. On a population basis NICE guidance recommends that vitamin D levels are not measured. Instead, they recommend blanket supplementation in the at-risk groups. Where vitamin D levels are measured defining a 'cut off' level that represents a clinically significant deficiency remains a challenge.

1.3.3 Prevalence of Vitamin D Deficiency in Crohn's Disease

We have previously published the results of a literature review on the prevalence of vitamin D deficiency in people with CD and UC (Fletcher and Swift, 2017, Fletcher et al., 2019). A narrative literature review was carried out to update this review with the aim of identifying prevalence of vitamin D deficiency in published primary peer-reviewed research using a Boolean/phrase, English language, title, and key word search of healthcare databases including PubMed, Cinahl plus, Medline (1946 to July 2019) and Web of Science Core Collection. Identified article titles and abstracts were

screened for inclusion. Inclusion criteria were peer reviewed primary research detailing measured levels of vitamin D in people aged more than 18 years who have diagnosed UC or CD. Papers were excluded if they were review articles, studies reporting only paediatric patients, studies related to non-IBD conditions, and studies that present data as IBD overall rather than CD and UC specifically.

The search terms used included prevalence AND vitamin D def* AND inflammatory bowel disease, and prevalence AND vitamin D def* AND IBD with alterations as required for each database. The terms 'inflammatory bowel disease' and 'IBD' incorporate MeSH terms that detect articles related to both CD and UC. Therefore, it was not necessary to search for each disease separately.

A total of six additional papers were added to results from our previous literature search (Fletcher and Swift, 2017) bringing the total to 13. Given the lack of agreement regarding a cut off levels data are shown for three different levels of 25(OH)D according to reported prevalence. Several studies present vitamin D deficiency rates as grouped data with both CD and UC presented as IBD. However, as this thesis relates specifically to CD only studies that presented CD data separately are included. Most studies used a cut-off of <50nmol/L to determine deficiency. Overall, the prevalence of vitamin D deficiency is greater in those with CD than UC and certainly higher than healthy controls in both CD and UC. It is interesting to note that there was only one UK study that met the criteria for inclusion. The map below (Figure 1-2) shows the countries that reported vitamin D deficiency levels colour coded according to the UVB intensity over the year. Those marked in the amber zone have UVB intensity thought to be insufficient for most of the year to induce vitamin D

synthesis (Tavera-Mendoza and White, 2007). Those coloured yellow are countries where UVB intensity is thought to be insufficient for at least one month of the year.

Figure 1-2: Countries reporting vitamin D deficiency. The amber zone indicates insufficient UVB light for most of the year and the yellow zone insufficient UVB light for at least one month of the year

From the studies included in Table 1-2, prevalence of vitamin D deficiency 25(OH)D <50nmol/l ranges from 6.6 to 100% (IQR 44-66%) in people with CD. The Lee et al (2018) and Kuwabara et al (2007) studies are outliers with reports of 6.6% and 100% prevalence respectively of patient vitamin D levels <50nmol/L. Kuwabara et al reported that over a third (n=10) of the CD patients included in the analysis were receiving enteral nutritional treatment. This suggests that their CD may have been particularly severe, with clinical malabsorption preventing intake of normal diet at the time of analysis and may explain the high prevalence of deficiency. In addition, their analysis is based on a small number of patients (n=29). In contrast the Lee et al.,

(2018) study reports a larger sample size (n=61) but specifically in pregnant women with CD. Their data, therefore, is skewed towards a healthier population and reports that most patients had well controlled disease at the time of pregnancy. Furthermore, some of the patients in the Lee et al., study were taking low dose vitamin D supplementation as advised in pregnancy. In the Kuwabara et al., study only dietary intake of vitamin D is recorded, suggesting that none of the patients were receiving supplementation at the time of analysis. These variances demonstrate the importance of understanding the patient's overall clinical picture in relation to their vitamin D status. Data from these studies are presented as published, however, meta-analysis might be possible in a planned future systematic review.

Table 1-2 Studies reporting the prevalence of vitamin D deficiency and insufficiency in Crohn's Disease and Ulcerative Colitis

Study & *country*	UC/CD	*n*	Mean age years (SD)	25(OH)D <75nmol/l (%)	25(OH)D <50nmol/l (%)	25(OH)D <30nmol/l (%)
Bours et al (2011) *Netherlands*	UC	185	50 (15)		34	
	CD	131	47 (15)		44	
Branco et al (2019) *Portugal*	UC	44	47 (17)		65	11
	CD	106			72	24
Caviezel et al (2017) *Switzerland*	UC	57	41 (13)		44	
	CD	99	41 (14)		58	
	IBS	25	48 (15)		28	
Chatu et al (2013) *UK*	UC	61	34 (14)		69	36
	CD	107			66	27
Frigstad et al (2017) *Norway*	UC	178	39		44	7
	CD	230	40		53	8
Gilman et al (2006) *Ireland*	CD	50	38 (10)		44	6
Hlavaty (2014) *Slovakia*	UC	43	47 (16)		97	69
	CD	97	38 (12)		92	74
Janssen et al., (2019) *Germany*	UC	121	43	24	55	
	CD	256		24	63	
Kabbani et al., (2016) *PA, USA*	UC	368	44 (10)	29.9		
	CD	597		30		
Kuwabara et al., (2009) *Japan*	UC	41	39 (15)		60	
	CD	29	32 (7)		100	
McCarthy et al., (2005) *Ireland*	CD	32	37 (11)		50	41
	HC	32	37 (11)		25	1
Lee et al., (2018) *Calgary, Canada*	UC	41	31.7 (3.5)	61	14.6	
	CD	61	31.2 (3.7)	50.8	6.6	
	HC	574	32.1 (4.3	17.4	2.1	
Pappa et al., (2006) *MA, USA*	UC	36	15 (3)			25
	CD	94	15 (4)			38
Sentongo et al., (2002) *PA, USA*	CD	112	16 (4)			16
Siffledeen et al., (2003) *Alberta, Canada*	CD	242	40 (10)		22	8
Suibhne et al., (2012) *Ireland*	CD	81	36 (11)	90	63	
	HC	70	36 (9)		51	
Torella et al., (2018) *Argentina*	UC	45	Median 41	62		
	CD	14		78		
	HC	56		21		
Ulitsky et al., (2011) *PA, USA*	UC	101	42	67	46	
	CD	403	43	76	51	
Veit et al., (2014) *MA, USA*	UC	18	16 (2)	83	50	28
	CD	40	17 (2)	73	40	15
	HC	116	15 (2)	75	27	10

UC=Ulcerative Colitis; CD=Crohn's Disease; IBS = irritable bowel syndrome; HC=Healthy Control.

1.3.4 Rationale for vitamin D supplementation in Crohn's Disease

In summary, there is emerging evidence that vitamin D has a significant role to play in CD but maintaining an adequate vitamin D intake via sun exposure or diet is unlikely to be feasible in this patient group, particularly in countries such as the UK where exposure to UV light may be limited year-round. Vitamin D supplementation may be a reasonable alternative to compensate for lack of sunlight synthesis of vitamin D. However, there is disagreement internationally on the optimal dose of vitamin D required to achieve this for the general population. There is little indication of how to supplement patients with malabsorption as seen in CD, and this is therefore an area of vitamin D health that requires further research.

Vitamin D deficiency is prevalent in the general population but more so in patients with IBD and particularly CD. Patients with IBD have been shown to have a high risk of developing osteoporosis and osteopenia, often diagnosed by bone mineral density (BMD) testing by DEXA scan, described in grams per centimetre. A cross-sectional study of 81 IBD patients (48 CD, 33 UC) and 81 healthy, controls used the trabecular bone score with DEXA to determine BMD. In this is study the definition for low BMD was as described by Shuhart et al., (2019) Low BMD was found in 49.3% of the IBD patients, compared with 23.4% of the healthy controls ($p = 0.001$). Fractures were detected in eight IBD patients (vertebral, $n = 5$; wrist, $n = 2$; hip, $n = 1$) and one control ($p = 0.01$) (Soare et al., 2021). Comparable results have been demonstrated in other studies (Lima et al., 2017) even in newly diagnosed IBD. Therefore, it is suspected that the inflammatory element of the disease is the primary influencing factor in low BMD and the development of osteoporosis, rather than treatments such as glucocorticoid steroids alone (Ezzat and Hamdy, 2010). A study of 124 patients UC

and 107 with CD, compared to 122 healthy controls, report that the UC and CD patients had lower vitamin D levels and a higher incidence of osteopenia and osteoporosis than controls (Tan et al., 2014).

Apart from the recognised benefits to bone health in maintaining optimal levels of vitamin D, there is the potential to influence the inflammatory activity of CD and improve clinical outcomes for patients, such as a reduction in CD symptoms and improved health related quality of life. However, much of the currently available data is observational and often conflicting in nature (Gubatan et al., 2019). A recent systematic review of observational studies including 27 articles with 8316 IBD patients (CD n=5210 and UC n=3115) considered the correlation between vitamin D status and IBD clinical outcomes. The meta-analysis showed that vitamin D deficiency is associated with clinical relapse, low quality of life scores, mucosal inflammation, and an increased risk of clinically active disease (Gubatan et al., 2019). Within the meta-analysis no single value was used to define vitamin D deficiency, rather the level used within individual studies and described as deficiency was used. The majority of studies used 25(OH)D <50nmol/L to define vitamin D deficiency, with a small number using 25(OH)D < 75nmol/L as the cut off. However, this correlation does not suggest that treatment of vitamin D deficiency would improve outcomes.

A meta-analysis of 18 RCTs of vitamin D supplementation in 908 patients with IBD showed that vitamin D supplementation reduced IBD relapse rates more significantly than in controls (Li et al., 2018). There were no other statistically significant differences demonstrated in terms of other clinical outcomes. Most of the studies included in the analysis did not stratify for disease (CD vs UC) except one. In this study Tan et al., (2018) randomised patients (CD n = 59, UC n = 65) to receive ether

vitamin D supplementation with calcium, calcium alone or no supplementation. There was no statistically significant difference in disease index scores in any of the arms for either CD or UC. The authors note that the dose of vitamin D supplementation was approximately 1667IU per day and suggest this may have been too low to show a therapeutic effect other than to increase vitamin D serum levels. Despite the number of RCTs reported in this meta-analysis, there is often inconsistency in trial design, the dose of vitamin D supplementation used and the inclusion of people who are not vitamin D deficient at baseline. Therefore, further well designed RCTs are likely to be of value (see section 4.2).

In clinical practice, where vitamin D deficiency is suspected or where there is a substantial risk of bone disease, such as with the use of corticosteroids, gastroenterology teams might consider blanket vitamin D supplementation in patients with CD without monitoring vitamin D levels (Lewis and Scott, 2007). It is unclear if vitamin D is monitored for patients where there are no risk factors other than their CD treatments. Our small retrospective audit of clinical practice showed that only 14% of patients with IBD had vitamin D screening carried out once in a 12-month period (Fletcher and Swift, 2017), despite growing suggestion of the non-skeletal benefits of treating vitamin D deficiency in this group (Fletcher et al., 2019). As such there is no standard practice in terms of checking vitamin D levels or standard of care in terms of dose or route of supplementation for this patient group (Fletcher et al., 2021a). There is a lack of clear national guidance in the UK regarding routine screening and the management of vitamin D deficiency in patients with CD, and a lack of clear compelling evidence of the non-skeletal benefits of this (Fletcher et al., 2021a). RCTs are needed to determine optimal 25(OH)D levels for patients with CD, how best to

treat deficiency in this patient group in terms of optimal dose of supplementation and determine whether this brings about improvements in patient reported outcomes. This would be a large undertaking involving multiple sites nationally or internationally. It is therefore an important first-step to undertake public and patient participation work and a feasibility study to determine whether and how a larger study should be conducted.

1.3.5 Research Question

Can vitamin D supplementation in people with Crohn's Disease improve symptoms as an adjunct therapy?

1.3.6 Projects

The plan of investigation for this thesis involved three main projects, utilising multiple research methodologies including:

- quantitative and qualitative survey
- observational cohort study
- randomised controlled vitamin D supplementation clinical trial

Project A: Current practice survey

A current practice survey was carried out to determine clinician's reported current clinical practice in vitamin D screening and treatment of vitamin D deficiency in patients with CD in the absence of clear national guidelines.

Projects B and C formed the parts of the two-part D-CODE Feasibility Study

Project B: Vitamin D screening prospective cohort study

A prospective observational screening study was conducted to identify the prevalence of vitamin D deficiency in CD patients at the Birmingham latitude in the UK and identify modifiable risk factors for vitamin D deficiency in this group of patients.

Project C: Feasibility study for a randomised controlled trial

A feasibility study for an RCT was conducted, identifying CD patients with vitamin D deficiency, and randomising them to receive one of two dose regimens of vitamin D supplementation. Improvement in CD symptoms was assessed via patient reported outcome measures. Biochemical measures were carried out to measure improvement in vitamin D levels and biochemical indicators of CD activity. For regulatory purposes this part of D-CODE was classified as a Clinical Trial of an Investigational Medicinal Product (CTIMP).

1.3.7 Dissemination Plan

Researchers have a responsibility to share the results of their research with as wide an audience as possible to ensure effective use of resources and research-based knowledge (Wilson et al., 2010). Dissemination of health-related research findings must reach healthcare professionals, key stakeholders in healthcare, other researchers, participants, and members of the wider public. The dissemination plan formed a core part of the NIHR funding application and was also referenced in the Research Ethics Committee (REC) application. In considering effective strategies for communicating results to the public, suggestions included a study Facebook page, a study website and liaising with relevant patient support groups and charities such as

Crohn's and Colitis UK. Suggested strategies were incorporated into the study dissemination plan (see Appendix 1).

1.4 Conclusion

Vitamin D deficiency is prevalent and likely to be more so in the CD population. There are likely benefits to vitamin D sufficiency and therefore a research study was justified. The plan of investigation followed a logical pathway in establishing current evidence and clinical practice, adding to the body of international evidence on prevalence of vitamin D deficiency in this group and, finally, exploring the feasibility of a future RCT to provide high-grade evidence for clinical management.

2 Project A: Current Practice Survey: vitamin D deficiency in Patients with Crohn's Disease; screening and treatment

Lead researcher: Jane Fletcher, Primary supervisor: Professor Fiona Irvine, Co-supervisors: Dr Amelia Swift, Professor Martin Hewison and Dr Sheldon Cooper

2.1 Introduction

Following review of the most current evidence available, the NICE Clinical Guideline CG152 regarding management of CD (2012) was updated and superseded in 2019 by guideline NG129 (2019). Neither of these versions refer to vitamin D deficiency in this high-risk group of patients. There is currently no UK national recommendation to direct medical teams to monitor CD patients for vitamin D deficiency. Several IBD clinical guidelines related to risk of osteoporosis in this patient group recommend blanket supplementation of vitamin D and calcium in patients receiving corticosteroid treatment due to the increased risks of bone disease associated with this treatment. However, monitoring vitamin D levels is not advocated in these key guidelines including guidelines from the British Society of Gastroenterology (BSG) (Lewis and Scott, 2007), European Crohn's Colitis Organisation (Van Assche et al., 2010) and the Gastroenterological Society of Australia (2018). Osteoporosis guidelines from the USA are one of the few that do recommend monitoring vitamin D levels in patients with IBD (American Gastroenterological Association, 2003). Additionally, a European clinical nutrition specialist group, the European Society for Metabolism and Clinical Nutrition, recommend that vitamin D levels should be monitored and supplemented in patients with IBD (Forbes et al., 2017).

Our previously published audit of IBD patients reviewed in a gastroenterology out-patient department suggested that vitamin D is not routinely monitored in local practice despite growing evidence of the benefit of this (Fletcher and Swift, 2017).

To aid future practice development, an understanding of influences and barriers to vitamin D screening in gastroenterology practice was required. Additionally, an exploration of current knowledge regarding vitamin D deficiency and treatment was warranted to aid education and information dissemination amongst gastroenterology teams. This current practice survey explored self-reported knowledge and clinical practice among clinicians who were members of the BSG.

The BSG is the major professional society for gastroenterologists and other healthcare professionals working within gastroenterology across the UK. It is divided into sections with specific interests. The IBD section has 985 members including medics, nurses, and other allied health professionals. These members were eligible to take part in the survey within the study period.

2.2 Literature Search

To identify published literature related to current clinical practice, a literature search using a Boolean/phrase, English language, all text search of healthcare databases was carried out. Databases included PubMed, Cinahl plus, Medline (1946 to July 2019), Web of Science Core Collection and Allied and Complementary Medicine Database. Identified article titles and abstracts were screened for inclusion.

Inclusion criteria: published papers detailing clinicians self-reported current clinical practice and/or attitudes towards vitamin D screening in people with CD or IBD and/or treatment of identified vitamin D deficiency.

2.2.1 Literature Search terms:

- Current practice AND vitamin D* AND Crohn*

- Current attitudes AND vitamin D* AND Crohn*
- Medical practice AND vitamin D* AND Crohn*
- Current practice AND vitamin D* AND IBD*
- Current attitudes AND vitamin D* AND IBD*
- Medical practice AND vitamin D* AND IBD*

2.2.2 Literature Search Results

Ten papers were identified in the search, but none met the inclusion criteria. None described clinicians' self-reported practice or attitudes towards vitamin D screening or treatment of deficiency in CD or IBD. All articles were either retrospective or prospective observational cohort studies or clinical guideline.

2.3 Research aims and objectives

2.3.1 Aim

Identify self-reported current clinical practice among gastroenterology teams in the UK in screening for and treatment of vitamin D deficiency in people with CD.

2.3.2 Main Study Objectives

- Use a web-based survey to gather information from healthcare professionals involved in caring for patients with CD
- Identify self-reported current practice in screening for vitamin D deficiency in patients with CD
- Identify self-reported current practice in treatments used to treating vitamin D deficiency in patients with CD
- Identify influences on current and future practice

2.4 Materials and methods

The study was a web-based survey involving healthcare professionals who are members of the BSG with an interest in IBD across the UK. The survey was designed using REDCap electronic data capture tools hosted at University of Birmingham (Harris et al., 2009). REDCap (Research Electronic Data Capture) is described as "a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources" (Harris et al., 2009). Study data was collected anonymously and managed using REDCap. Access to data on REDCap was password protected with permissions given only to JF and the supervisory team.

2.4.1 Survey Design

Survey questions were created in collaboration with the supervisory team. Overall, the purpose was to elicit information on normal screening practice and treatment of vitamin D deficiency, and factors that might influence practice (see Appendix 2). Specific key areas of interest identified were:

a) whether participants thought that vitamin D levels should be routinely measured in people with CD

b) if not, why not

c) what their usual practice was in terms of frequency of screening for vitamin D deficiency in CD for given sub types of CD and given CD treatments

d) awareness of any guidelines related to vitamin D in people with CD

e) factors that might influence the decision to screen such as season, patient ethnicity or other socio-economic or cultural factors

f) if they did not currently screen for vitamin D deficiency, what might influence their future practice

g) what treatments might they recommend for various levels of vitamin D deficiency if detected

h) any other nutritional monitoring and investigations into bone health they might routinely carry out

i) demographic details to include geographic location and area of work.

2.4.1.1 Questions

The survey comprised a total of 20 questions with six branching logic questions. The number of questions was purposely kept low to encourage participation and completion (Burns et al., 2008). Of these, 19 out of 26 questions were multiple choice and seven were free text. Though open ended/free text questions allow for greater data collection, the data collected may also be more difficult to analyse, hence this type of question was used primarily to allow the participant to expand on a previous answer. Multiple choice questions (MCQ) were used in preference for ease of data completion and analysis. At least five options or more were offered on each MCQ to improve quality of data (Knapp, 2018).

Three questions were presented in matrix format as the most succinct way to present multiple options (Liu and Cernat, 2016). However, these were kept to a minimum as

this format is slightly more likely to lead to missing data than single item questions (Liu and Cernat, 2016).

2.4.1.2 Completion time

Completion time was anticipated to be five to ten minutes for participants. Studies have shown that survey time of less than 13 minutes is optimal in improving response rates (Fan and Yan, 2010). Features enabled within the REDCap data capture tool included the option to save and return, allowing participants greater flexibility in completing the survey. Additionally, the completion bar was enabled to indicate what percentage of the survey they had completed.

2.4.1.3 Survey Pilot

After the survey was drafted, it was piloted with five Consultant Gastroenterologists at QEHB to test the functionality of the software and user-friendliness of the survey. There were no functional problems identified and no amendments suggested by the pilot group.

2.4.2 Survey Distribution

With the agreement of the Chair of the BSG-IBD section, survey distribution was performed by the BSG communications team via email to members of the IBD section. The email included a link the online REDCap survey (https://is.gd/crohnsvitD). Emails were sent by the BSG-IBD chair on 16th March 2019 and again approximately two weeks later. The survey was also advertised on the 'News' page of the BSG website. Participants were asked to complete the survey any time within one month, allowing them time to consider if they wished to participate. The survey closed on 15th April 2019.

2.4.3 Eligibility Criteria

Inclusion

- Members of the BSG IBD section who are all health professionals with a declared interest or role in management of IBD.
- Those who gave informed consent by agreeing to participate

Exclusion

- Those not invited to participate via the BSG

2.4.4 Sample size calculation

A sample size calculation was carried out using the online sample size calculator www.calculator.net. A confidence level of 95% was used to measure how accurately the sample size would represent the intended population i.e., 95% confident that the sample size would be representative. The population size was 985 and the online calculator suggested a sample proportion of 50%. With these parameters sample size was calculated as n=277.

Web-based surveys in healthcare research typically have a response rate of approximately 30-35% (Cunningham et al., 2015). Purposive sampling was used to include all members of the BSG-IBD. This was to ensure that all registered members with a specific interest in IBD had the opportunity to take part.

2.4.5 Statistical analysis

Data were exported from REDCap to Microsoft Office Excel™ 2010 software for analysis and production of tables and graphs. The online calculator: www.knowpapa.com/sd-freq/ was used to calculate standard deviations.

Results are presented using descriptive summary statistics including frequencies, percentages, and standard deviation (SD) for grouped data where appropriate. The proportion of missing values are assessed. Qualitative responses are collated into common themes (Fletcher et al, 2020).

2.4.6 Data Sharing

A data management plan was developed, describing which data were to be collected, how it would be collected, organised, and stored according to regulatory requirements (see Appendix 3). For data sharing purposes, data is stored in the UBIRA open access repository hosted by University of Birmingham: https://doi.org/10.25500/edata.bham.00000363

2.4.7 Ethics

University of Birmingham Ethical approval was received (ref: ERN_19-0128**).** The survey was distributed to healthcare professionals within their professional role. It was assumed that participants had capacity to consent. The opening page of the electronic survey detailed participant information and consent (see Appendix 2). No personal identifiable data was collected within the survey. Participants completed electronic consent by 'agreeing' to participate and confirming that they had read and understood the information.

2.5 Results

Circulation of the survey was to approximately 985 clinicians. However, only 200 of the eligible clinicians clicked into the survey, 75 consented and a total of 62 clinicians completed the survey (Table 2-1). Most respondents were Gastroenterology Consultants and primarily affiliated to university teaching hospitals.

Table 2-1 Demographics and response rate of the current practice survey

Response rate	**n (%)**
Survey circulation*	985
Consented/initiated survey	75 (7.6)
Entered data	64 (6.5)
Completed data entry	62 (6.3)
Click rate*	200
Click rate response	64 (32)
Respondents	
Gastroenterology Consultants	48 (77)
Gastroenterology Registrars	11 (18)
Registered Nurses	3 (5)
Institution/affiliation	
University Teaching Hospital	36 (58)
District General Hospital	25 (40)
Primary Care	1 (2)
Age	
30-39 years	13
40-49 years	19
50-59 years	27
60-69 years	3
Mean age (SD)	43 (8.6)

*While the survey was circulated to 985 clinicians there is no way of confirming if it was received by all. The click rate provides a useful indication of the number who received the survey and viewed it. It is unclear why some consented but did not enter data, but this may be because that they had to consent in order to view the survey content.

All participants in the 30-39 years age range were Gastroenterology Registrars. Two registered nurses were in the 50-59 years and one in the 40-49 years range. The majority of Gastroenterology Consultants were 50-59 years (n = 25, 40%), with relatively few in the 40-49 years group (n = 18, 29%) and in the 60-69 years group (n = 3, 5%).

The geographical location of respondents is shown in Figure 2-1. The highest number of responses were received from participants in the Midlands (England) (19%), North West England (18%) and South East England (16%). There were no responses from Wales.

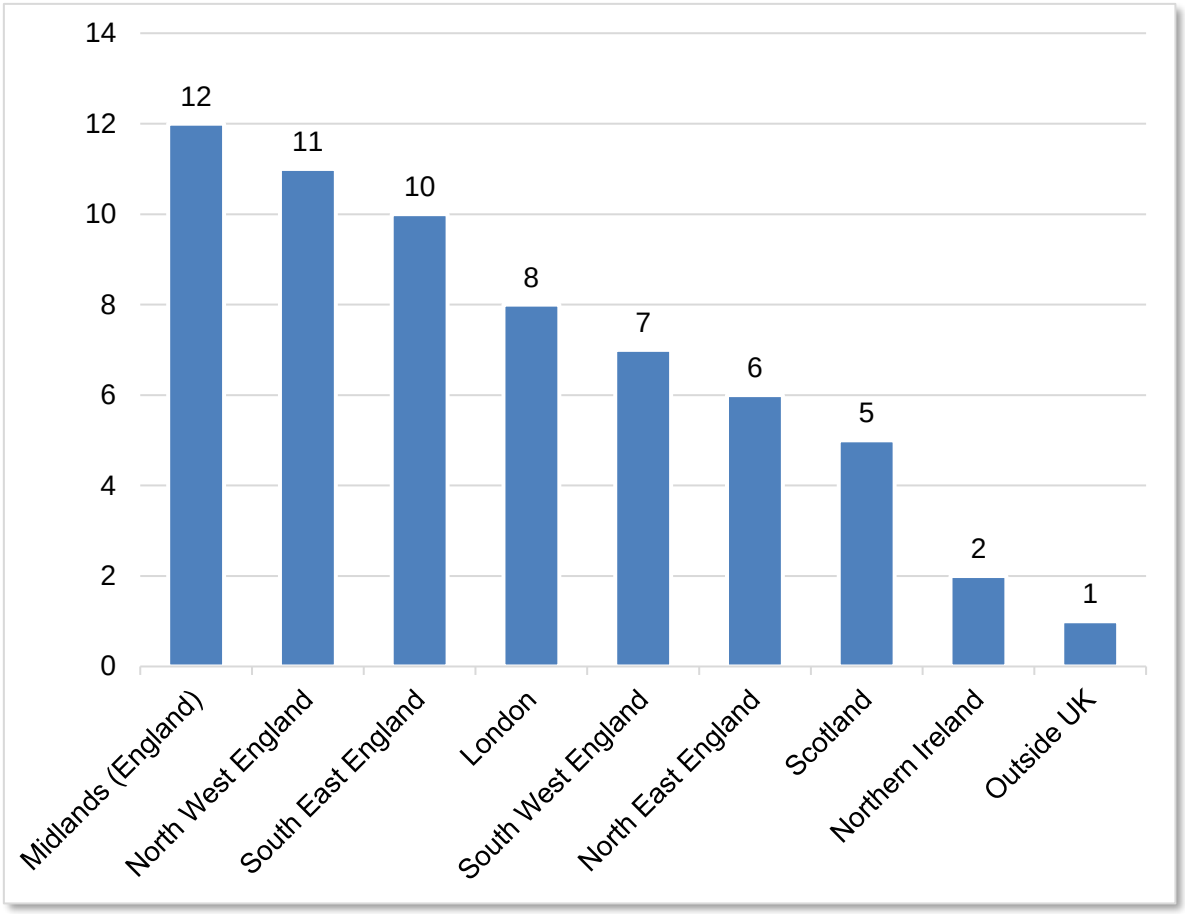


Figure 2-1: Reported geographical location of respondents (n = 62). There were responses from a wide geographical area within the UK. The majority of respondents were from the Midlands and North West of England. There were no responses from Wales.

2.5.1 Vitamin D Screening in Practice

The sub-types of CD described in the survey were small bowel CD, CD colitis and perianal CD. Screening was most likely to be carried out annually and most often in those with small bowel CD (Figure 2-2).

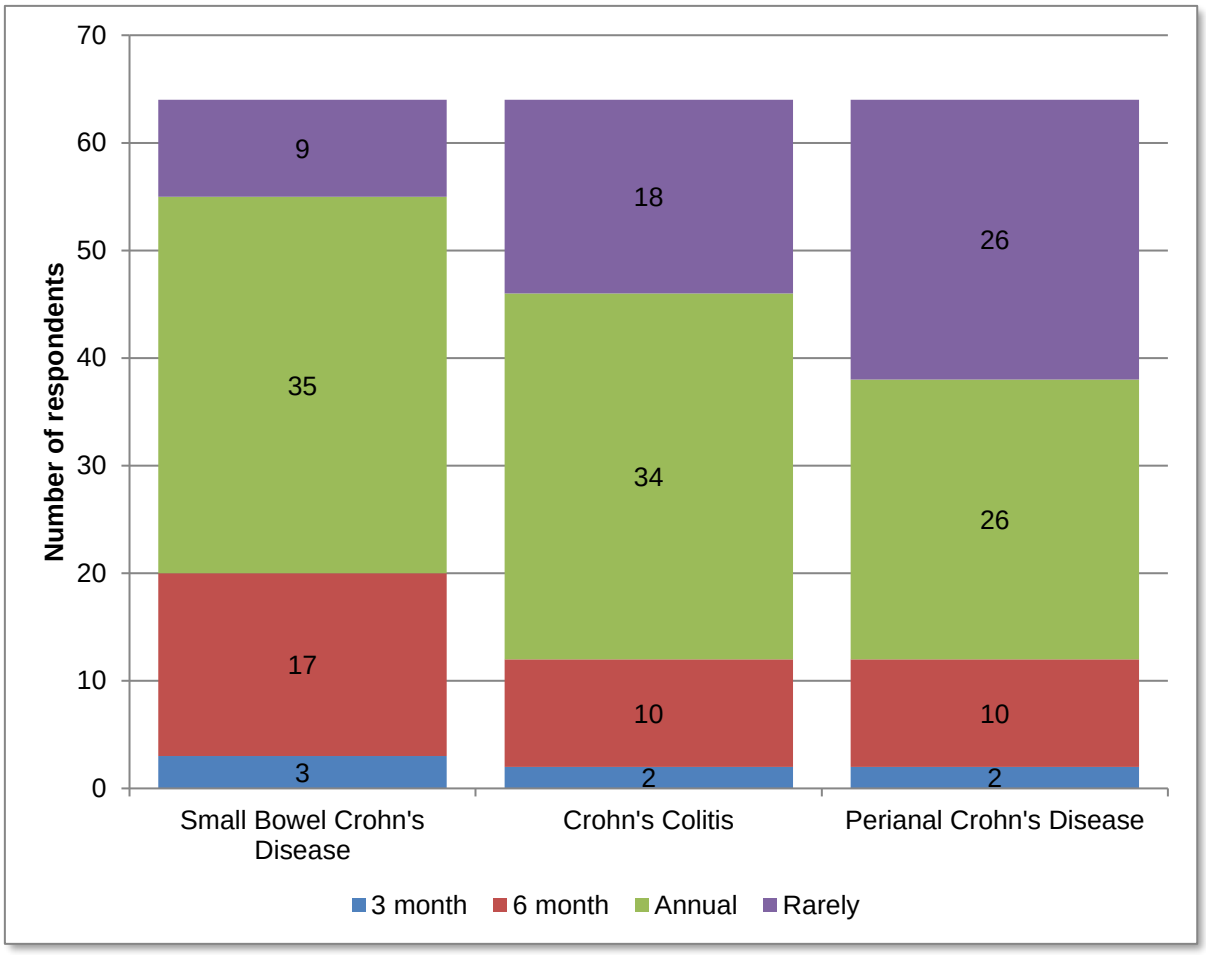


Figure 2-2: Reported frequency of vitamin D screening by Crohn's Disease sub-type. Screening was most likely to take place annually for all sub-types of Crohn's Disease, but most likely in those with small bowel disease followed by those with Crohn's colitis.

Common therapies for CD management included immunomodulators, biologic therapies, steroids, and surgery. Screening was most likely to be carried out annually and in those with a history of previous surgery related to their CD (Figure 2-3).

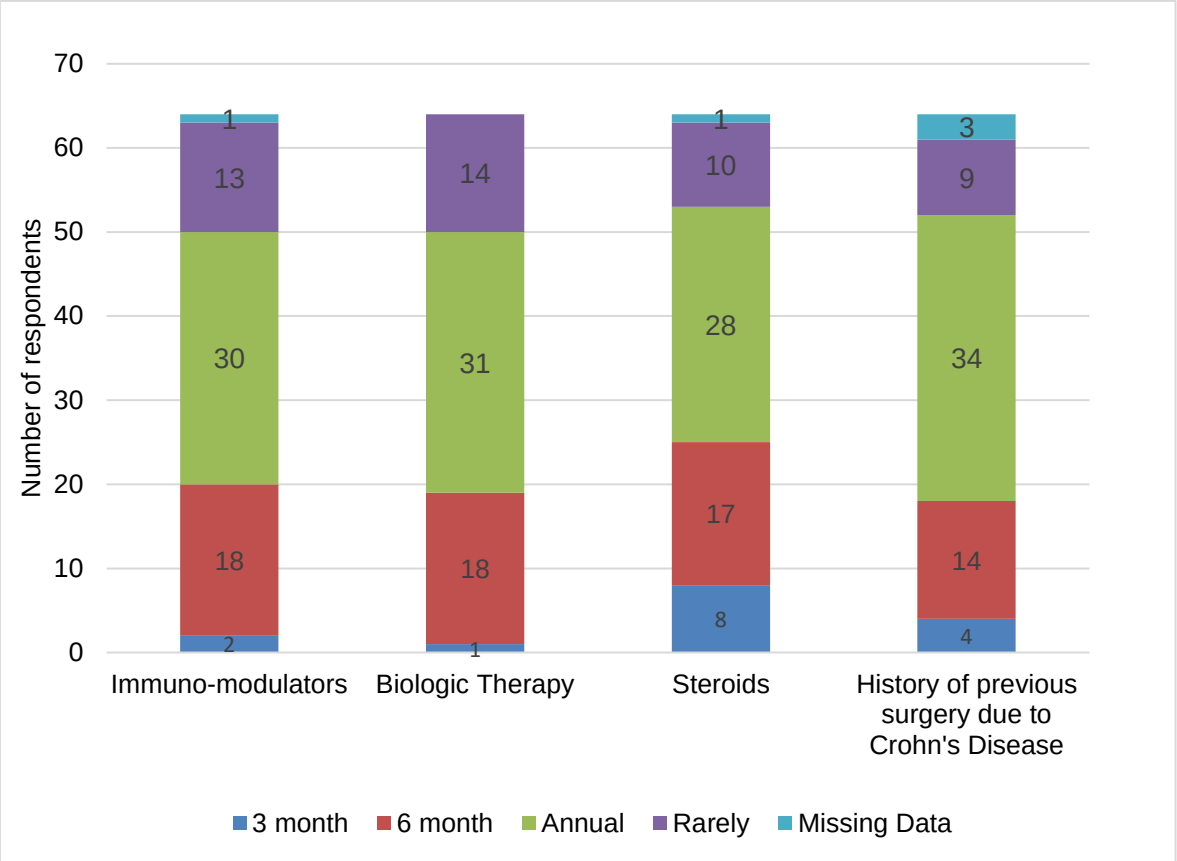


Figure 2-3: Reported frequency of vitamin D screening by therapy. Screening was most likely to take place annually in all therapy groups, with patients having a history of surgery related to their Crohn's Disease the main indicating factor.

In terms of influences of ethnicity or season of the year on decisions to carry out vitamin D screening, in total, 15/64 (23%) respondents were more likely to check vitamin D levels in those from an Asian background or with darker skin. A minority (n=19, 29.7%) were more likely to check levels according to the season. Free text comments included one who stated they were *more likely to remember in the winter/spring,* and one who said they were *more likely to check in winter* and *lack of sun exposure*.

Other socio-economic or cultural influences given were that screening would take place in those who covered their body completely for religious reasons (n=5), those thought to have poor nutrition or low socio-economic status (n=1) and those following a restricted diet such as vegan (n=1).

2.5.1.1 Awareness of Guidelines

Respondents were aware of several guidelines which they thought were related to vitamin D and CD including European Crohn's Colitis Organisation (ECCO) (n = 11), British Society of Gastroenterology (BSG) (n = 5), other osteoporosis guidelines including those from USA (n = 3), nutritional societies including UK, European and USA (n = 1), local guideline (n = 1), and NICE (n = 1) (Fletcher et al, 2020). It is notable that some of the identified guidelines are not related to vitamin D deficiency in patients with CD or IBD specifically, for example NICE and most osteoporosis guidelines.

Figure 2-4 shows reported other factors that were likely to influence clinical practice in vitamin D screening. There were several factors likely to influence screening practice the main being better evidence (n=25) and clear guidance (n=23).

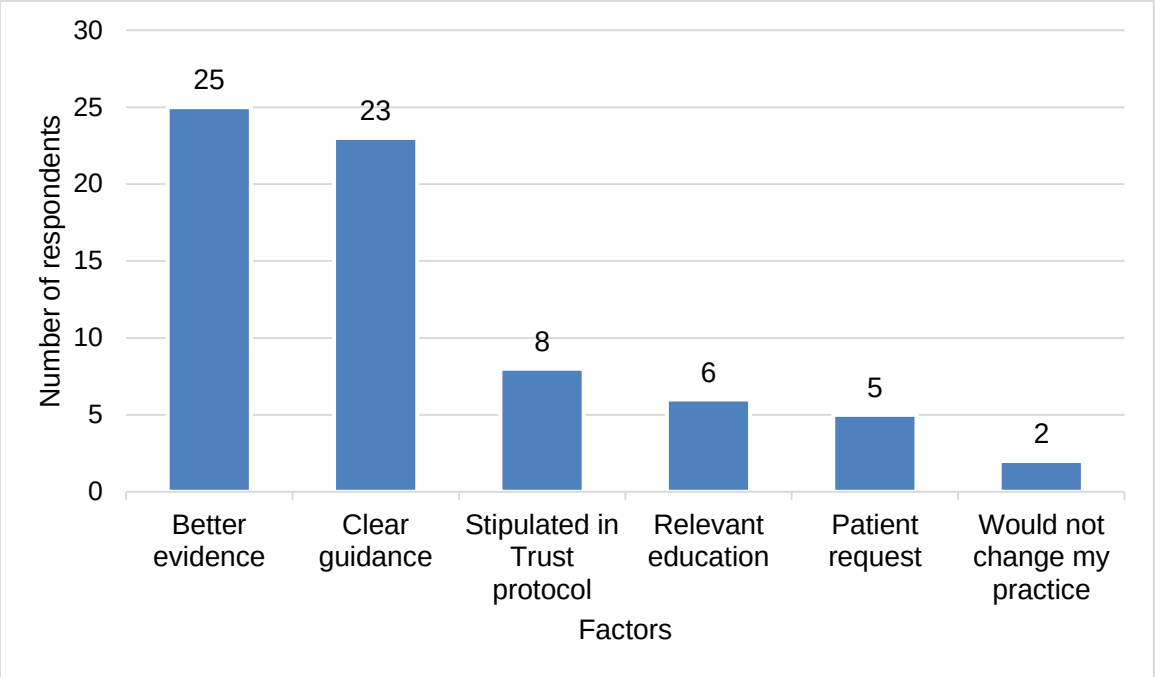


Figure 2-4 Factors likely to influence clinical practice in vitamin D screening. Respondents identified better evidence and clear national guidance as the two key factors most likely to influence their practice in screening for vitamin D deficiency in Crohn's Disease. Note that respondents were able to select multiple factors.

2.5.2 Treatment of Identified Deficiency

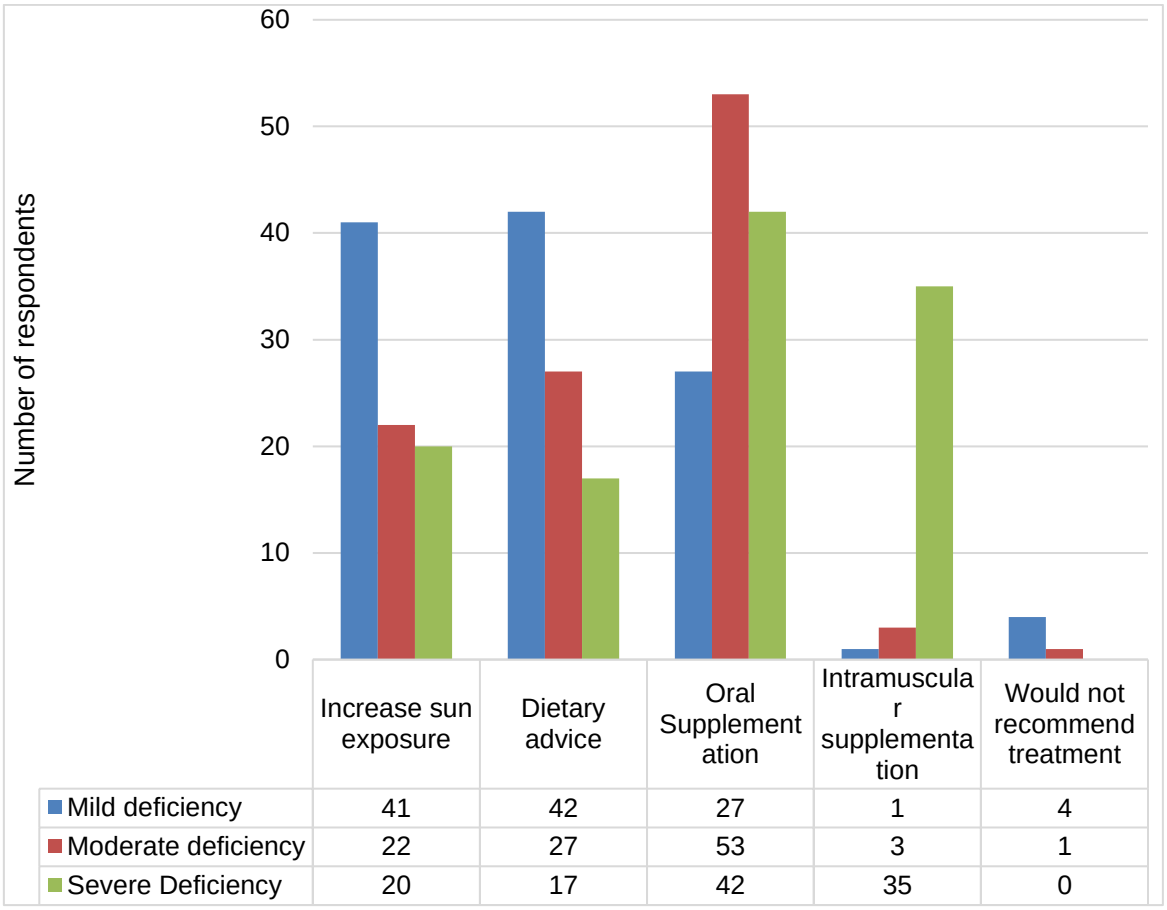
Several different treatments for vitamin D deficiency were used according to level of deficiency (mild 35-49nmol/l moderate 15-34nmol/l, or severe 0-14nmol/l,) with results shown in both a table format and graphically (Table 2-2 and Figure 2-5). Possible treatments included advice on increasing sunlight exposure, dietary advice to increase intake of vitamin D from food, oral supplementation, or intra-muscular supplementation. Sunlight and dietary advice were most likely to be given for mild deficiency with supplementation most likely to be given for moderate to severe deficiency in reported clinical practice. Intramuscular supplementation appeared to be most favoured in severe deficiency, nevertheless, one respondent reported they would consider intramuscular supplementation even in mild deficiency. Only a small

number (n=4) of respondents would not offer any advice or treatment for mild deficiency and moderate deficiency (n=1). All respondents would recommend treatment in severe deficiency.

Table 2-2: Frequency of treatments offered in the management of vitamin D deficiency

Treatment	Vitamin D level nmol/L	Frequency (%)
Increased sunlight exposure (n=83)	0-14	20 (25)
	15-34	22 (27)
	35-49	41 (49)
Dietary advice (n=86)	0-14	17 (20)
	15-34	27 (31)
	35-49	42 (49)
Oral supplementation (n=122)	0-14	42 (34)
	15-34	53 (43)
	35-49	27(22)
Intramuscular injection (n=39)	0-14	35 (89)
	15-34	3 (8)
	35-49	1 (1)
No treatment (n=5)	0-14	0
	15-34	1
	35-49	4

Data is also presented in a graphical format in figure 2-5. Note that respondents were able to select multiple treatments for each level of deficiency.



	Increase sun exposure	Dietary advice	Oral Supplementation	Intramuscular supplementation	Would not recommend treatment
Mild deficiency	41	42	27	1	4
Moderate deficiency	22	27	53	3	1
Severe Deficiency	20	17	42	35	0

Figure 2-5: Treatments used in the case of identified vitamin D deficiency in people with CD. Increasing sun exposure and dietary advice was most likely to be given in those with mild vitamin D deficiency. Oral supplementation was most likely to be given in moderate deficiency with intramuscular supplementation considered in those with severe deficiency. Few respondents said they would not recommend treatment in mild and moderate deficiency. Note that respondents were able to select multiple treatments for each level of deficiency.

2.5.3 Monitoring of Nutritional Markers and Bone Health

Respondents were asked to note any other nutritional markers they were likely to measure in patients with CD given the known likelihood of nutritional difficulties with the disease. Iron studies and vitamin B_{12} were most likely to be measured (n=58) (Figure 2-6).

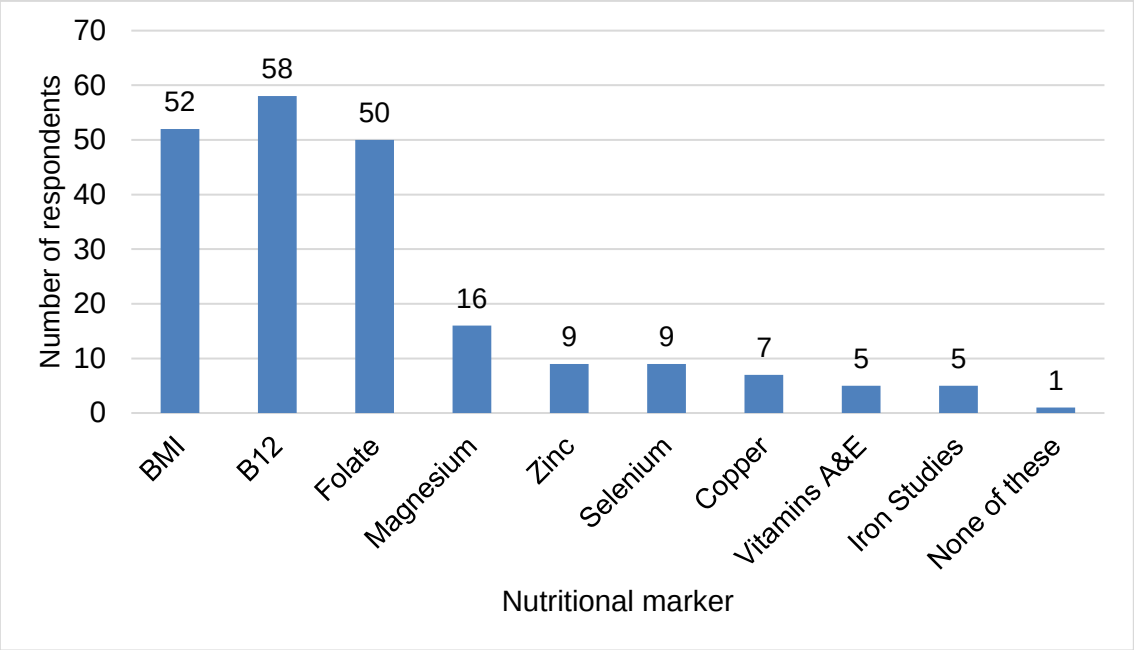


Figure 2-6: Measurement of nutritional markers in Crohn's Disease. A variety of other nutritional markers were likely to be monitored in patients with Crohn's Disease, primarily Vitamin B_{12} and folate, often related to anaemia in Crohn's Disease, and body mass index (BMI). Note that respondents were able to select multiple nutritional markers.

Figure 2-7 indicates factors that would lead clinicians to investigate bone health. A history of steroid use was the prevailing factor recorded (n=57) with malnutrition being a further key factor (n=44).

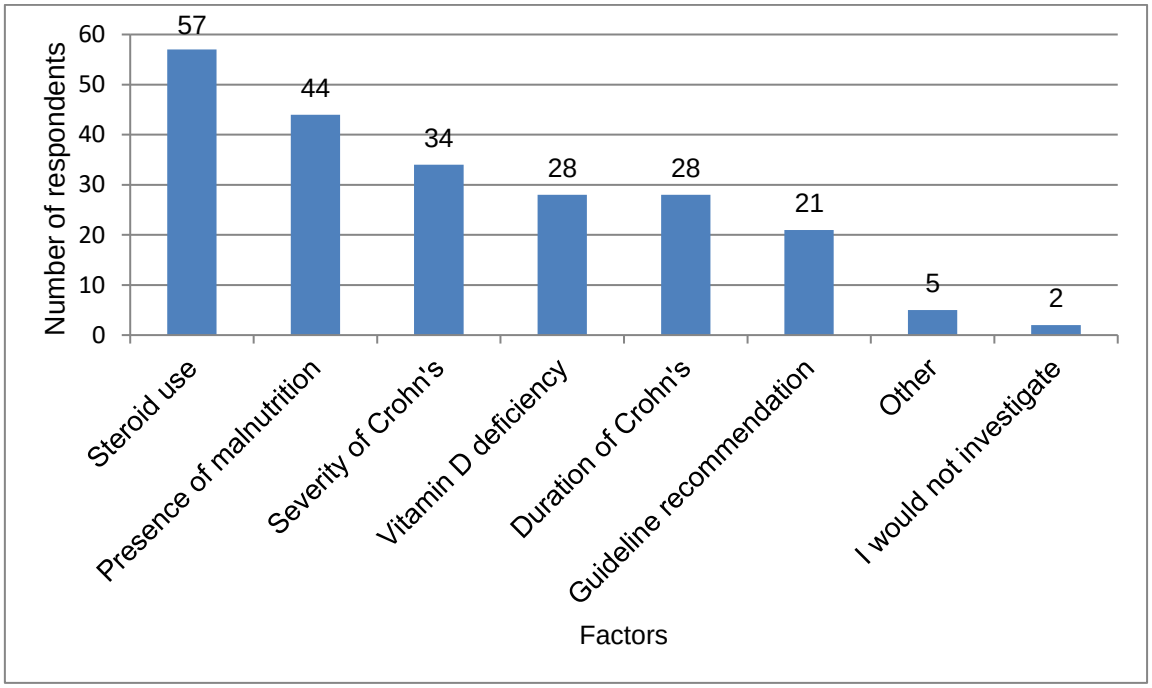


Figure 2-7: Factors influencing investigations into bone health in Crohn's Disease. Steroid use was the factor most likely to lead to investigations into bone health in patients with Crohn's Disease, followed by malnutrition. Note that respondents were able to select multiple factors.

2.6 Discussion

This current practice survey set out to identify vitamin D screening and management behaviours in clinicians providing management for patients with CD. The response rate was relatively low but there was relatively broad geographic coverage. The findings suggest that most respondents are carrying out vitamin D screening in patients with CD at least annually. Screening is more likely to be performed for those who have had previous surgery related to CD and in those with small bowel CD. This is despite the lack of clear national guidance to carry out vitamin D screening in people with CD. It is possible that respondents are using published literature as reference points to guide practice, such as Nielsen et al., (2019). Results also may

suggest that respondents consider these sub-groups to be at higher risk. Other risk factors for vitamin D deficiency, including ethnicity, season, lack of sun exposure, and poor nutritional status, were also considered by respondents and were likely to result in vitamin D screening being undertaken.

Nutritional parameters, including BMI, vitamin B_{12}, and folate were commonly measured with iron studies and vitamin B_{12} most likely to be measured. This may be due to the known risk of anaemia seen in CD and the causative factors of iron or vitamin B_{12} deficiency (Madanchi et al., 2018) being recognised by clinicians. The risk to bone health of recurrent steroid use was recognised with most respondents reporting that they would investigate bone health further in this group.

In terms of treatments for vitamin D deficiency, oral supplementation was most frequently indicated by respondents for treatment of moderate vitamin D deficiency, whereas increasing sun exposure and dietary advice were mostly selected in mild deficiency. The level of evidence for different treatments was not explored in this survey. Nevertheless, the clinician's perception of efficacy of different treatments is of interest. For example, the preference for intramuscular supplementation in severe vitamin D deficiency suggests that clinicians perceive intramuscular to be more effective than oral supplementation in severe deficiency. Conversely in mild vitamin D deficiency, dietary advice with no supplementation was most likely to be used. Nielsen et al., (2019) suggest a useful approach to vitamin D supplementation in patients with IBD, considering several factors, including level of deficiency, disease activity, and malabsorption. The results of this survey imply that some clinicians are already following some of the strategies suggested by Nielsen et al., (2019), including

screening annually, supplementation with oral or intramuscular preparations as required and increased sunlight exposure to manage vitamin D deficiency.

The literature search conducted before the survey suggests that this is the only current practice survey focusing specifically on self-reported practice in vitamin D screening in people with CD in the UK. Wagnon et al., (2009) report a USA survey of gastroenterologists' implementation of the American Gastroenterological Association (AGA) guidelines on osteoporosis in IBD where vitamin D supplementation was covered as part of osteoporosis management and assessment. Twenty-one per cent of respondents reported that they recommend vitamin D and calcium supplementation to all patients with IBD. Screening patients for vitamin D deficiency prior to supplementation was not included in the survey (Wagnon et al., 2009), although measuring vitamin D is recommended by AGA (2003) in this patient group.

The measurement of vitamin D serum levels may be contentious, being deemed costly and inaccurate by some groups (Lewis and Scott, 2007). Indeed, one respondent in the current practice survey commented that their Trust did not allow vitamin D serum levels to be measured if a patient had a normal serum calcium level (Fletcher et al, 2020). With many guidelines advocating standard, blanket vitamin D 800-1000IU daily and calcium 500-1000mg daily supplementation of patients receiving corticosteroids (Lewis and Scott, 2007, Van Assche et al., 2010, Gastroenterological Society of Australia, 2018), it could be argued that monitoring levels is unnecessary and standard supplementation could be advised for all. One survey respondent commented that they thought all patients with CD were at risk of vitamin D deficiency. However, this is rarely the case: although prevalence of

deficiency is high, it is unusual for all reported cases to be deficient as seen in Table 1-2, where only one study reported 100% deficiency amongst included patients.

A greater understanding of specific risk factors in sub-types of CD is required for those working with patients clinically. Those with small bowel CD are likely to be at higher risk of deficiency than those with peri-anal disease, for example, due to bile salt malabsorption seen when the terminal ileum is affected by CD (Uchiyama et al., 2018). Other lifestyle and ethnic factors will also have an impact on individual risk of deficiency. It would be clinically unnecessary, and therefore a waste of healthcare resources, to supplement people who are unlikely to benefit from it. Although, generally considered to be safe, Taylor and Davies (2018) describe the risks of vitamin D toxicity from incorrect prescribing, dispensing and self-administration of high dose vitamin D supplements. Conversely, if low doses of supplementation are taken then they may have limited positive effect in increasing serum levels. For example, low dose (400IU) vitamin D supplementation was compared to high dose (4000IU) in a double blind, randomised controlled trial of vitamin supplementation in patients (n=41) with pre-hypertension (Zaleski et al., 2015). Mean 25(OH)D levels were similar between the groups pre-treatment (39.2 ±SD15.7 nmol/mL; $p \geq 0.05$) and increased by 11±SD18nmol/mL and 40±SD26.7 nmol/mL respectively after 6 months of supplementation. Although the effect of the low dose supplement was less than the high dose, it must be recognised that the low dose did increase vitamin D serum levels from deficiency (<50nmol/L) to sufficiency in this patient group overall. In terms of doses of vitamin D in a malabsorptive disease such as CD, it is difficult to predict a standard dose that all patients will benefit from without monitoring the effect of supplementation. In a small randomised trial of 39 patients with CD, low dose

(1000IU) vitamin D supplementation was compared to high dose (10,000IU) in raising serum levels of 25(OH)D after 12 months of supplementation (Narula et al., 2017). In this patient group, levels increased from 71.3 nmol/L+SD7.3 to 82.8 nmol/L+SD26.3 ($p = 0.63$) and from 73.5nmol/L+SD11.7 to 160.8 nmol/L +SD43.2 ($p = 0.02$) respectively. The low dose achieved a much smaller increase in serum levels; however, it must be noted that the participants in this study were not vitamin D deficient at baseline. In addition, there is lack of consistency between test doses between trials. Despite vagaries with the assay and disagreement over cut off points, monitoring vitamin D levels as 25(OH)D is currently the most reliable method of establishing individual deficiency and monitoring effectiveness of treatment.

2.6.1 Limitations

The main limitation in this survey was the response rate despite efforts to promote good uptake in terms of survey design and mode of distribution.

2.6.1.1 Survey Design

Several aspects were considered in the design of the survey to promote participant response. A web-based survey delivered via email is an acceptable and recognised method of collecting information from healthcare professionals (Cunningham et al., 2015). E-mail delivery has the advantage that it remains until purposely deleted, thus it is less likely to be mislaid than a paper- based survey. The survey was active for one month, allowing participants adequate time to complete it. A reminder was sent after approximately two weeks of the initial distribution. Cook et. al., (2000) note that excess reminders tend not to increase responses. Distribution of the survey was via the BSG as a professional, reputable society relevant to the population (Fletcher et al., 2020). It is notable that 40 surveys were completed within the first two days of the

reminder being sent with numbers tailing off over the final two weeks. There were no further data entered in the two days preceding survey closure.

In a systematic review and meta-analysis of 20 studies, Rolstad et. al., (2011) found that survey length was significantly associated with response rate, with longer surveys having a poor response rate ($p = 0.0001$). However, the authors advise caution concluding that response rate cannot solely be attributed to survey length. In this study, survey length was a consideration with the number of questions kept purposely small to reduce the burden to participants.

2.6.1.2 Survey distribution

The distribution method was a key limitation of this survey despite the strategies taken to improve response rate. The BSG is a respected professional society and the use of a third party to distribute the survey ensured anonymity for participants. However, it is noted that the click rate and the number of responses received, in comparison to the number of members in the BSG-IBD section, is not representative of the overall group. It is likely that those who responded were clinicians with an interest in vitamin D and, therefore, their practice may not reflect gastroenterology practice across the UK or among BSG members generally. With the survey being distributed by the BSG the study team had no control over the technical aspects of the distribution and therefore cannot determine with confidence how many members received the survey email (Fletcher et al., 2020). For this reason, the “click rate” (n = ~200) reported by the BSG communications team was used as a more reliable indicator of the number of people who received and viewed the survey. This was used to calculate the response rate of 32%, based on the number of people who clicked in to the survey and entered data.

This response rate is within the average of 30–35% anticipated for web-based surveys involving healthcare professionals (Cunningham et al., 2015) but significantly lower than other surveys distributed via professional organisations to a similar audience. A Europe wide web-based survey containing 32 questions regarding the structure of training programmes on paediatric endoscopy had a response rate of 62% (Broekaert et al., 2019). The survey was open for 19 months with monthly reminders sent via email and was also distributed via a professional society (Young ESPGHAN) (Broekaert et al., 2019). A web-based survey in the UK, comprising eight questions regarding diathermy practice for colonic polypectomy, achieved a 71.8% response rate (Verma and Chilton, 2019). This survey was open for 8 months and was circulated via three different e-newsletters by the BSG. The authors do not state how many times the survey was distributed. Hence, the two main differences between the administration of these surveys and the current survey were, firstly, the length of time the survey was open and, secondly, the number of reminders sent. However, it could be argued that the topic, vitamin D deficiency, of the current survey was the predominate factor impacting response rate.

Fan and Yan (2010) suggest that the relevance of the survey topic to the audience is one of the main influencing factors on response rate. The published surveys by Broekaert et. al., (2019) and Verma and Chilton (2019) relate to core skills in endoscopy required in the role of a gastroenterologist. In the UK specialty curriculum requires only an awareness of osteoporosis in specific disease states, and vitamin D deficiency is not mentioned at all (Joint Royal Colleges of Physicians Training Boards, 2010). It is likely that some recipients did not find the topic of vitamin D deficiency in CD of relevance or interest to them. Nevertheless, a repeat of the

current practice survey would be required over a longer period and with multiple reminders to validate this theory. However, any repeat of the survey may be more helpful when further evidence regarding vitamin D supplementation in patients with CD is available.

Other published surveys regarding practice in the management of vitamin D deficiency amongst diverse groups of healthcare professionals have achieved an equally poor response. A web-based survey distributed to members of the Dietitian Association Australia via their weekly online state newsletter received an approximate 3% response rate (134/ <4000) (Dix et al., 2017). This survey was also open for 28 days. From the 134 responses received, the authors concluded that dietitians in Australia had a good understanding regarding food sources of vitamin D but that there was confusion regarding treatment of vitamin D deficiency, supplementation and sun exposure and (Dix et al., 2017).

2.7 Conclusion

It can be assumed that the respondents to the current practice survey were those gastroenterologists with an interest in vitamin D deficiency, and therefore they represent a highly selected and biased sample. Only 14% of respondents reported that they rarely/never monitor vitamin D in CD (Fletcher et al., 2020). The key reasons cited for not monitoring vitamin D in this patient group were a lack of national guidance and a lack of evidence. It is widely recognised that the key benefit of vitamin D is related to skeletal health. However, vitamin D supplementation has proven to be of benefit in other disease states, for example, in reducing the incidence of breast cancer (Mcdonnell et al., 2018), non-skin cancer in women aged over 55 years

(Mcdonnell et al., 2016) and respiratory tract infections (Martineau et al., 2017). In addition, in women with 25(OH)D concentrations maintained ≥100 nmol/L compared to those with 25(OH)D levels <50 nmol/L, a 60% lower preterm birth risk was observed (Mcdonnell et al., 2017).

Definitive evidence is required to inform national guidance and avoid disparity in clinical practice. There is a need for well conducted clinical trials in patients with identified vitamin D deficiency to inform guidance. Such clinical trials should take into account the principles set out by Heaney (2014) in the design and the analysis of nutrient based clinical studies (Fletcher et al., 2020).

3 Project B: Vitamin D Status of People with Crohn's Disease and Modifiable Risk Factors: a prospective observational screening study

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3.1 Introduction

Data related to the prevalence of vitamin D deficiency in people with CD in the UK is limited with only one published study to date (Chatu et al., 2013). In this study of 168 patients with IBD (107 CD and 61 UC) in London, Chatu et. al., (2013) found a 68% prevalence of vitamin D deficiency (serum 25(OH)D <50nmol/L) across the study population. The authors note that deficiency was highest in non-White study participants. While the prevalence and incidence of CD has generally been highest in White populations, there is evidence that cases are increasing in other ethnic, particularly migrant, groups in the USA and UK (Cosnes et al., 2011, Mukewar et al., 2013, Misra et al., 2018). A recent UK, prospective cohort study collected data on newly diagnosed IBD cases over a year, in areas of the UK with a high proportion of the population from South Asian background. They found that incidence of CD cases in different ethnic groups were: White European 6.5, Indian 4.7, Pakistani 3.1 and 'Other' 1.5 per 100,000 cases (Misra et al., 2019).

Birmingham is a large, ethnically diverse city at a northerly latitude. Data from the 2011 Census suggests that 57.9% of Birmingham residents report their ethnicity as White British or 'Other White' with the remaining 42.1% of residents coming from other ethnic groups (Table 3-1). A further census was carried out in 2021 but the full results of this are not yet available.

Table 3-1 Ethnic diversity in Birmingham according to 2011 Census data

Ethnic group	Birmingham population number	Birmingham population by %	England comparison %
White British	570,217	53.1	79.8
Pakistani	144,627	13.5	2.1
'Other' ethnicity	71,680	6.7	3.1
Indian	64,621	6.0	2.6
White other	51,419	4.8	5.7
Caribbean	47,641	4.4	1.1
Mixed	47,605	4.4	2.3
Bangladeshi	32,532	3.0	0.8
African	29,991	2.8	1.8
Chinese	12,712	1.2	0.7
Total	1,073,045		100.0

(Birmingham City Council, 2021)

Ethnicity is recognised as a risk factor for the development of vitamin D deficiency in people with CD (Fu et al., 2012). With a large population of non-White residents, investigation into the vitamin D status of patients with CD in Birmingham was warranted.

Lifestyle or modifiable risk factors for vitamin D deficiency, such as diet and sun exposure (Tolppanen et al., 2012), are of interest in considering treatment and prevention of deficiency in all ethnic groups. In the current practice survey (section 2.0), gastroenterologists reported that they may consider dietary and sun exposure advice in the management of mild to moderate vitamin D deficiency in patients with CD (Fletcher et al., 2020). However, dietary intake of vitamin D in patients with CD, and IBD generally, has been found to be sub-optimal (Vidarsdottir et al., 2016, Lambert et al., 2021) and usually below that of healthy controls (Lambert et al., 2021). In a systematic review, Lambert et. al., (2021) identified 40 studies that collated information related to CD patients' overall dietary intake but none of these had considered intake of vitamin D containing foods specifically. Hence, analysis of likely

vitamin D intake was limited. Given that there are differences in overall habitual dietary intake of patients with IBD compared to healthy controls (Peters et al., 2020); an understanding of the intake of key vitamin D containing foods is important to understand dietary risk factors for vitamin D deficiency in this group.

In terms of sun exposure, an Italian case-control study (Vernia et al., 2018) of 292 people with IBD (132 CD and 160 with UC) assessed sun exposure of those with IBD against healthy controls using criteria recommended by Glanz et al., (2008). People with IBD were more likely to have low to moderate levels of sun exposure compared to controls. People with CD were more likely to have low to moderate levels of exposure compared to those with UC. Furthermore, there is debate regarding the effect of sunscreen lotions on the cutaneous production of vitamin D when people do have adequate sun exposure. While a global consensus group suggests that the use of sunscreen does not affect vitamin D levels in healthy individuals, they acknowledge that in specific groups there is an increased risk (Passeron et al., 2019). Situations likely to compromise vitamin D status include the use of high sun-protection factor (SPF) sunscreens with high UVA protection, along with shade-seeking behaviour and covering the skin with protective clothing (Passeron et al., 2019). People with CD may be advised to take all these precautions when prescribed thiopurines due to the increased risk of non-melanoma skin cancer noted with these medications (Magro et al., 2014, Setshedi et al., 2012, Huang et al., 2019). Hence sun exposure and use of SPF are relevant to risk of vitamin D deficiency in this group. Smoking status of patients is also of interest as smoking has been found to be associated with vitamin D deficiency (Nwosu and Kum-Nji, 2018, Banihosseini et al., 2013, Ren et al., 2016).

A previous cross-sectional study of 58 patients with CD in Ireland explored lifestyle and behavioural influences on vitamin D deficiency, but with a focus on vitamin D supplement use (Gilman et al., 2006). Information collected regarding sun exposure was not detailed. Results showed no correlation between lifestyle factors and vitamin D status; however, this may have been due to the routine use of vitamin D supplementation in the study group. A further exploration of key modifiable risk factors in patients with CD was justifiable.

3.2 Aims

Primary

To determine the prevalence of vitamin D deficiency measured by total 25(OH)D in adults with CD in Birmingham, UK (latitude 52.47867° N, -1.90848° E).

Secondary

- To identify lifestyle factors including diet, sun exposure and smoking that may influence vitamin D status in patients with CD in Birmingham
- To identify participants for recruitment to the D-CODE vitamin D supplementation study

3.3 Methods

3.3.1 Study design

The vitamin D screening study was a prospective study conducted during different months of the year in patients with confirmed CD. The screening study was the first part of the wider D-CODE Feasibility study (Fletcher et al., 2021a); with regulatory approvals from the REC and MHRA gained within the D-CODE Feasibility Study as described in the following chapters. The Strengthening the Reporting of

Observational Studies in Epidemiology (STROBE) statement guidelines (Von Elm et al., 2008) are used in the reporting of this study.

3.3.2 Setting

The study was designed to be carried out at three hospital sites that are all part of University Hospitals Birmingham NHS Foundation Trust (UHBFT) including

i) Queen Elizabeth Hospital Birmingham (QEHB) a large tertiary referral centre,
ii) Birmingham Heartlands Hospital (BHH) a large secondary care centre, and
iii) Good Hope Hospital (GHH) a district general hospital.

The three hospitals are in the south, east, and north of Birmingham. The greatest ethnic diversity is seen in populations served by QEHB and BHH however, BHH area serves greater numbers of patients from ethnic minority groups. Using these three sites would give an effective indication of vitamin D status among different ethnic and socio-economic groups across Birmingham.

3.3.2.1 Site opening

Due to logistical issues, BHH and GHH sites were not opened for recruitment. Although BHH and GHH had confirmed capacity and capability for the study, they were unable to provide a suitable clinic room/area for study participants to be seen. Therefore, the study was opened at QEHB only.

3.3.3 Patient and Public Involvement

Patient and public involvement (PPI) in research refers to public participation, not as the subjects of research, but as research partners. The NIHR (2019a) has a focus in PPI in all aspects of research design and conduct. In this way the quality, scope, and

relevance of research for people affected by research, i.e., patients and service users, may be improved. A recent survey found that 91.5% (n = 65) of responding UK surgical studies reported to have included PPI, with the most common PPI activity being the design of participant information (72%) (Crocker et al., 2019). Arguments in favour of PPI include the ethical right of patients and the public to be involved in developing research that affects them and that PPI will improve clinical and healthcare research (Wicks et al., 2018).

Over recent years the value of PPI in research has become apparent with patients and service users often bringing unique lived experience of their condition and valuable alternate perceptions (Mcgillion et al., 2018, Domecq et al., 2014). However, it is important to acknowledge that some researchers find PPI difficult and an additional burden within their research that causes them some apprehension (Thompson et al., 2009). In qualitative interviews with 36 health researchers, Boylan et al (2019) found researcher attitudes to PPI included both enthusiasm and cynicism. Interviewees described the emotional and practical burdens involved from their standpoint but also the rewards and relationship-building benefits. Although PPI is a requirement for many funders and RECs (Fleurence et al., 2013, National Institute for Health Research, 2014), there is still scope to improve its meaningful adoption in research. A survey of 251 researchers found that around three quarters of respondents thought it was ‘very important’ or ‘fairly important’ that service users were involved in all stages of research. However, they identified a sizeable minority who viewed PPI with more scepticism (Becker et al., 2010). Hence, evaluating and reporting the benefits versus costs of PPI are important to engage the research community in meaningful PPI (Boivin et al., 2018).

A randomised-cluster trial of patient involvement (n=83) in setting health research priorities for chronic disease management, showed that researchers/professionals (n=89) alone tended to focus on the technical aspects of disease management. In contrast, patients placed importance on more general aspects such as access to primary care, support, and patient participation in clinical decision-making ($p < 0.01$) (Boivin et al., 2014). These alternate opinions are important in ensuring that research is relevant to those affected by the conditions being studied and the interventions being proposed.

In the RAPPORT study, Wilson et al., (2015) found that reports of PPI activity included improvements to study design, improvements to recruitment materials and recruitment rates, and dissemination of research results. A recent systematic review and meta-analysis by Crocker et al., (2018) showed that PPI modestly but significantly increased the odds of participant recruitment in included studies (OR 1.16, 95% CI 1.01 to 1.34). In a review of mental health research studies (n=374), Ennis and Wykes (2018) found that studies involving PPI to a greater extent were more likely to achieve recruitment targets defined as 90% of the target ($p <0.05$). These findings are supported by earlier systematic reviews (Domecq et al., 2014). Ennis and Wykes (2018) suggest that the improvement in recruitment seen with PPI may be due in part to the language used in materials such as information sheets being easier to understand when written by or influenced by other lay people. In addition, patients contribute insight into the realities of living with a health problem and therefore understand which methodology is likely to be the most acceptable to study participants. An earlier systematic review of 66 published articles identified key themes in relation to the positive impact of PPI: including clarifying academic

language, assisting with recruitment via community contacts and assessing the appropriateness of research measures and instruments (Brett et al., 2014).

The study design phase is a key period for PPI when members of the public and patients may have the greatest influence on the research question and study design (Boote et al., 2010). Within both Project B and C, PPI was essential in the research design, study conduct and monitoring. However, key challenges were sourcing funding for pre-award PPI activities and identifying people to participate in the PPI group.

3.3.3.1 Funding for Initial PPI Activity

NIHR funding requests must include realistic costs that enable effective and meaningful PPI within the research project. However, PPI was required at the design stage of the research proposal and, so, prior to a research funding application. The NIHR recommend that PPI members are paid for their time as research partners in recognition of their contribution. There were also costs incurred for travel expenses, refreshments, meeting room bookings/videoconferencing and printing. Financing the cost of PPI at this stage then presented a challenge. In 2016, 400GBP was awarded from the NIHR PPI Bursary to cover the costs of the initial PPI meeting and activity. This was a competitive bursary that the NIHR provided to enable pre-funding award PPI to take place. Currently there are other similar funds available in the UK via Research Design Service (RDS) Public Involvement Funds (Research Design Service West Midlands, 2019).

3.3.3.2 Identifying PPI Group Members

There is often a general assumption that PPI members should be representative of the study population to represent their interests in research (Guarino et al., 2006). However, Boote et al., (2010) dispute this and argue that the expectation for members of the public to represent other people with similar health experiences places an unreasonable burden on them. Boote et al., suggest that the purpose of PPI is to seek patient and public perspectives rather than any form of representation; an individual can only represent themselves. This view is further supported by Staniszewka et al., (2012) in their current opinion piece on PPI in the development of patient reported outcome measures. Nevertheless, identifying lay people who are interested in being research partners is a challenge. A few approaches may be taken including:

- Advertising the project on an open forum such as the NIHR People in Research website (2019b). On this website members of the public can find projects requesting public involvement.
- Approaching existing PPI groups within an organisation (Hull et al., 2012).

Both approaches rely on members of the public who are actively seeking to collaborate in research. In their review, Crocker et al., (2019) report that approximately 13.8% of studies recruited via established PPI groups and around 7.7% recruited PPI members via an open invitation such as a website. A key disadvantage of this method is that people tend to come forward from specific backgrounds, predominately White, middle-class and retired (Health Experiences Research Group, 2019). Volunteers often have a certain level of social capital and educational attainment that gives them the confidence to engage with research

teams, and they might also have a medical background (Health Experiences Research Group, 2019). Therefore, they may not share the same, or even similar perspectives to an ‘average’ patient.

Other patients and service users, who might have never considered research involvement, have insights that are valuable to research development (Fletcher et al., 2021c). Engaging with these groups requires an alternative approach including:

- Patient support groups and charities passing on information about relevant research projects (Heaven et al., 2016).
- Researchers advertising at a more local level, for example within clinical areas and outpatient departments, requesting service users to make contact.
- Researchers contacting patients and service users directly inviting participation.

A personal, direct approach was used to identify service users who might be interested in collaboration in the studies. This method is consistent with findings from other clinical trials that found that overall, 61.5% of studies reported using a direct invitation to recruit patients/service users to their PPI groups. Most often group members were identified from those who had previously collaborated in PPI (18.5%) and patients known to the clinical team (49.2%) (Crocker et al., 2019).

3.3.3.3 Expert by Experience – IBD Group

The Expert by Experience - IBD group was convened in 2016 prior to the initial NIHR fellowship funding application. The aims were

- to comply with NIHR PPI requirements for funding

- to gain insight from the group regarding the feasibility of the proposed study methodology from a patient's perspective (both in the screening study and later feasibility clinical trial).
- establish the importance and relevance of the proposed research question to patients

Using NIHR Involve resources (Hayes et al., 2012) and advice from the Research Application Service at UHBFT, it was decided that approaching patients known to JF would be an appropriate strategy to identify PPI collaborators, and one that had been shown to be effective in other studies (Crocker et al., 2019, Gazzard et al., 2018, Foster et al., 2016). The patients known to JF were those identified from a specific cohort of patients, who had a severe form of intestinal failure and were on long term treatment under the care of JF. Within this group were patients with IBD who had been service users for several years, and so were experts within their own health and disease (Department of Health, 2001, Tattersall, 2002).

Seven patients with IBD were identified from the group and all were invited to form the PPI group. A personal letter was sent to each patient describing the initial outline for the study and how their experience would be valuable in designing the project. The letter stated that their care and clinical relationship would not be affected in anyway if they chose to participate or not. A reply slip and prepaid envelope were included. Patients invited were from a range of economic backgrounds including unemployed, employed, and retired. None of those invited were known to have a medical background or to have participated in PPI previously. At the time of invitation there were no IBD patients within this cohort from a Black or minority ethnic group and none with a known disability.

3.3.3.3.1 Demographics of the PPI group

Of the seven invitations sent, three patients responded positively (female n = 2, male n =1. Employed/self-employed n=1, unemployed n =1 and retired n=1) and one patient responded that they did not have time to participate. All participants were White British. One respondent asked if their male spouse could join the group, and this was agreed as a useful addition to the membership. Carers and relatives and carers of people with chronic diseases may experience the impact of the disease in different ways (Bottomley et al., 2013) and so have alternate perspectives to contribute. The results of the PPI meetings have been integrated in the relevant methods sections to show how their advice informed choices.

3.3.3.4 PPI contribution to study development

The Expert by Experience - IBD group continued to collaborate on the study development once research funding was granted and the protocol and Research Ethics Committee (REC) application was in progress. Their key activities included commenting on the lay summary for the REC application, commenting on and editing the participant information leaflets, and designing a poster to advertise the study in out-patient areas (Fletcher et al., 2021c). The PPI group decided to take sole responsibility for poster design to ensure the overall message was patient-friendly (See Appendix 5). The ongoing activity and contribution of the group was consistent with other published evaluations of PPI outcomes (Wilson et al., 2015). The Expert by Experience -IBD group continued as core members of the Trial Management Group (TMG, see section 4.6.2).

3.3.4 Study Recruitment

The first recruitment period was September 2019 – January 2020 in the Gastroenterology clinics at QEHB. Due to the COVID-19 pandemic, after March 2020 few patients attended hospital for routine face to face appointments. However, patients were still attending out-patient infusion units for essential CD treatment. Subsequently, the second recruitment period took place in November- December 2020 in the infusion unit at QEHB.

3.4 Participants

3.4.1 Eligibility Criteria - Inclusion

- Those identified by their clinical team as having a confirmed diagnosis of CD
- ≥ 18 years of age
- Those who provided written informed consent

There were no exclusion criteria.

3.4.1.1 Participant identification

3.4.1.1.1 Gastroenterology Clinic and Infusion Unit

With agreement from Gastroenterology teams, Gastroenterology/IBD clinic lists were reviewed on the UHBFT IT system to identify patients with CD who were due to attend clinic within the recruitment period. No list or database was available at the time to identify patients who have IBD or CD, nor is there a specific clinic for IBD. Therefore, records were scrutinised for all clinic attendees to find those who had a confirmed diagnosis of CD according to their Gastroenterologist's clinic letters. The date and time of their attendance was noted, and each was approached in clinic by the clinical

team, who discussed the screening study with patients to identify eligibility and interest in participation.

Infusion unit visits are managed by the IBD Nursing Team. Patients were identified from the IBD nurse weekly infusion list, with eligibility confirmed by the principal investigator (SC) or other medically trained doctor. Patients were approached on arrival for their infusion appointment.

For those who consented to participate at their Gastroenterology out-patient or infusion unit appointment, all study procedures and data collection were completed within the same visit. This reduced the requirement for patients to return for a separate study visit and so reduced the burden to them. However, participants were free to return another day for participation if they preferred.

3.4.2 Consent

The patient information leaflet (Appendix 7) was posted to patients prior to their normal follow-up clinic or infusion unit appointment to allow them adequate time to consider the information before being approached for consent to participate at their appointment. Informed written consent was gained prospectively from participants during their outpatient visit.

3.4.3 Data Management

Data management, including data base development and data analysis, was delegated to the clinical trials unit (CTU) by the study Sponsor. The data management plan was developed by CTU data managers, information systems and statisticians, and retained at the CTU.

3.4.4 Confidentiality

Participants were identified by a three-digit screening number on the case report form (CRF) that was sent to the CTU to maintain confidentiality. In addition, date of birth was recorded to allow CTU monitoring of eligibility criteria (those aged 18 years or over) and act as a second point of identification. All data collected and sent to the CTU for entry on to the study database, was stored on University of Liverpool servers with access restricted to CTU team members identified on the CTU study delegation log. These servers are in an access-controlled server room and are connected to the main University network, located behind a security system. Physical access to these servers is limited to members of the University's computing services department. At the CTU, paper CRFs and questionnaires were stored within a locked area at the CTU, accessible only to authorised staff. A list of screening numbers linking to patient identity was maintained within the study site file held at QEHB. Site files were kept in a locked office and only accessible to members of the team named on the QEHB study delegation log.

3.5 Outcome measures

The primary outcome measure was total 25(OH)D serum level and the presence of deficiency defined as <50nmol/L. Data on lifestyle/modifiable risk factors including consumption of vitamin D containing foods, vitamin D supplements, sun exposure, use of SPF and smoking were collected verbally from participants.

The screening study ran concurrently with the D-CODE feasibility clinical trial, with participants for the feasibility trial identified from the screening study. For that reason, additional data relevant to eligibility for the vitamin D supplementation clinical trial was also collected, although this was not specifically relevant to the screening study.

This data included if participants had medical conditions or were taking medications listed in the exclusion criteria for the feasibility clinical trial. The purpose of this was to ensure that participants, who were identified to have vitamin D deficiency but who were otherwise ineligible for the clinical trial, were not contacted inappropriately regarding the trial.

3.5.1 Vitamin D Dried Blood Spot Test

City Assays Sandwell and West Birmingham NHS Trust www.cityassays.org.uk developed a commercially available, assay for measuring 25(OH)D in whole blood dried onto a blood spot – termed a dried blood spot (DBS) test. The results have been aligned with their serum/plasma standardisation so that results can be directly compared with conventional vitamin D reference ranges. Vitamin D in the screening study was measured using the City Assays finger prick sample collection kit which is CE marked.

The DBS is designed as a home testing kit and the initial plan was to post the kits to selected patients for them to administer at home. However, a member of the PPI group tried the testing kit and felt that it was not user-friendly. The PPI group identified a risk that the test would not be carried out correctly, affecting the reliability of results. Study methodology was revised so that JF would attend the outpatient department/infusion unit to discuss the study with patients and administer the DBS test in person. The PPI group suggested benefits of this were i) more confidence from patients in the study and reliable results from the blood test being correctly administered ii) Assurance that the test had been completed. Participants were unlikely to complete the test at home unless they were very motivated, thereby

impacting on recruitment iii) Increasing participant confidence. Participants would have less confidence in the study if the test were sent via the post.

Sample collection kits (see Appendix 8 for an image of the kits) were stored at room temperature as per manufacturer's instructions. Considering manufacturer's instructions, the process followed for completing the sample collection was:

i) Attach a study label with the participant's unique identifier (screening) number, date of birth and gender to the assay kit form. No other identifiable information was entered onto the form.

ii) Record participant's identifier number, date of birth and sample collection date on the blood spot collection card.

iii) Identify finger to be bled (middle or ring finger) and massage from the palm towards the tip.

iv) Cleanse the fingertip area with the enclosed cleansing wipe and allow to dry to remove any contaminants.

v) Remove the cap of the single use lancet by twisting.

vi) Press the white tip of the lancet to the side of the cleaned finger. With gentle pressure deploy the lancet and pierce the finger.

vii) Wipe the first spot of blood away with a clean piece of lint free gauze.

viii) Gently squeeze the finger to stimulate blood flow. Add one large drop of blood by gravity onto each of the designated four areas indicated with an arrow on the blood spot collection card. Circles indicated the size of the blood spots required on the card. The manufacturer stressed that the fingertip must not be pressed to the card.

ix) Cover the puncture wound with a sterile plaster.

x) Place the assay kit form and blood spot collection card into the provided prepaid envelope and post the same day.

The blood spot 25(OH)D assay was performed by Black Country Pathology Services, located at Sandwell General Hospital, West Bromwich, UK. Concentrations of the two forms of vitamin D (25(OH)D2 and 25(OH)D3 were measured in dried blood spot eluates using liquid chromatography tandem mass spectrometry (LC-MS/MS) (Waters Acquity UPLC – TQS or TQS-Micro Mass Spectrometer) after derivatization and liquid–liquid extraction of the blood spot eluates, as previously described (Shea and Berg, 2017). All blood spot samples were analysed in duplicate and mean concentrations of 25(OH)D2 and 25(OH)D3 calculated. The assay was calibrated using in-house material such that the dried blood spot 25(OH)D concentrations produced are equivalent to serum 25(OH)D concentrations. The between day coefficients of variation are 11.1% at 16.9 nmol/L 8.2% at 45.5 nmol/L, 6.9% at 131.7 nmol/L and 7.0% at 222.2 nmol/L for 25(OH)D3 and 13.7% at 18.1 nmol/L, 7.5% at 42.7 nmol/L and 6.4% at 127.3 nmol/L for 25(OH)D2. Limits of quantitation are 7.5 and 2.8 nmol/L for 25(OH)D3 and 25(OH)D2 respectively. The mean bias of dried blood spot *versus* serum 25(OH)D3 concentrations over the period 2018 to 2021 was 4.0%. This suggests that the dried blood spot may slightly overestimate 25(OH)D3 concentrations compared to a serum sample. The laboratory is accredited to ISO15189 and participates in the UK NEQAS for Vitamin D and the Vitamin D External Quality Assessment Scheme (DEQAS) for serum 25(OH)D. Results were emailed securely and confidentially via an nhs.net email set up for the study UHB.dcodetrail@nhs.net. Participants and their G.P. were informed of the vitamin D result in writing by JF.

3.5.2 Demographic Data

Participants indicated their ethnic group from 18 listed categories as per the Office for National Statistics (2017). Sex at birth and date of birth were gathered from their hospital records.

3.5.3 Crohn's Disease Status

Participants indicated if they thought their CD was active or in remission. Active disease was defined as active without treatment, or currently having treatment that was controlling their symptoms. The participants were asked to estimate what year their CD was diagnosed to gain an indication of disease longevity from the patient's perspective.

3.5.4 Food Frequency Data

Food frequency data was collected from participants to identify overall consumption of key vitamin D containing foods described by NHS England (2017). Intake was identified by frequency of food consumption over a week rather than specific portion sizes. Frequency was defined as: Rarely (0), 1-2 Times, 3-4 Times, 5 or more times per week. Foods were listed to patients verbally and their answer recorded for each food.

The key vitamin D containing foods were:

i) Oily fish (such as salmon, sardines, herring, mackerel)
ii) Red meat
iii) Liver or offal
iv) Eggs including the yolk

v) Foods that are labelled as fortified with Vitamin D (such as breakfast cereal, spread etc.)

Participants recall of their normal weekly intake of identified foods was used, instead of a specified recall period, to reduce the risk of bias from any recent, short-term variations in diet. Participants were asked if they were taking any over-the-counter vitamin D, fish oil or multi-vitamin supplements; or having vitamin D containing supplementation prescribed by a healthcare professional as a further indication of likely vitamin D intake. Responses were either yes or no, doses and frequency were not recorded for those who responded yes.

3.5.5 Sun Exposure

The PPI group identified that sun exposure such as holidays would impact on the vitamin D result and should be considered. Questions regarding recent travel to a sunny country, use of sun lotion, SPF and the amount of skin usually exposed to the sun was added to the case report form to capture these data.

Participants described their likely clothing if they were out in the sun on a warm day to indicate likely sun exposure. Categories were listed verbally as follows:

i. Shorts and a short sleeve top
ii. Long trousers/skirt and a short sleeve top
iii. Keep arms and legs covered
iv. Keep whole body completely covered

Skin type was ascertained in relation to how easily participants perceived their skin tanned. Categories were listed verbally as follows:

i. Tan or darken easily

ii. Go red then tan

iii. Burn

Participants indicated if they wore sun lotion with SPF and if so, what SPF they usually used.

Smoking was recorded as a yes/no answer to indicate current smoking habits.

All collected data was recorded and transcribed on to the CRF to be sent to the CTU for database entry and data analysis.

3.6 Bias

The inclusion criteria were intentionally broad, with no exclusion criteria, to reduce selection bias. Any adult patient with CD attending their usual Gastroenterology follow up appointment or infusion unit appointment at QEHB was eligible. As all study procedures took place at the same appointment there was no bias from loss to follow up.

3.7 Study size

As the screening study was part of the D-CODE feasibility clinical, and not a standalone study, the sample size for the screening study was based on the number likely to be required to achieve adequate recruitment for the D-CODE feasibility trial. Therefore, no formal sample size or power calculation was carried out for the screening study alone.

As the clinical trial was a feasibility study it was not powered to detect a difference and no formal sample size calculation was carried out by CTU statisticians (see

section 4.4.2 for further information on the CTU). The initial aim was to recruit 50 patients to the feasibility clinical trial divided between the three identified sites. To recruit 50 patients in the trial, 250 patients across the three sites were estimated to be needed in the screening study to allow for the following:

- Moderate estimate that only 50% of screened patients are likely to have vitamin D deficiency based on previous vitamin D deficiency literature
- 20% of patients with vitamin D deficiency are likely to be ineligible for the vitamin D supplementation trial due to exclusion criteria
- Estimate that 50% of eligible patients would not provide consent to participate in the vitamin D supplementation trial (Fletcher et al., 2021a)

3.7.1 Screening Study Site Sample Size

Target sample size for each site was planned as follows:

i. QEHB – screening study 100 participants (aim to randomise 20 in the clinical trial study)
ii. BHH – screening study 100 participants (aim to randomise 20 in the clinical trial study)
iii. GHH – screening study 50 participants (aim to randomise 10 in the clinical trial study)

A further brief period of screening was planned at a different time of year to determine seasonal differences in vitamin D status, and the impact this would have on recruitment in a longer running RCT. The overall target sample size for this was 50 participants (QEHB 20, BHH 20 and GHH 10). As previously mentioned, only QEHB

site opened to recruitment. Therefore, as a single site study, the total screening recruitment target was n=120.

3.7.2 Future study sample size calculation

In a future repeat of the screening study, a formal sample size calculation would be carried out for statistical confidence. According to the Office for National Statistics (ONS) Birmingham's resident population was estimated to be 1,141,400 in 2018 (Birmingham City Council, 2019). Allowing a North European estimate of 262 prevalence per 100,000 population for CD (Ng et al., 2017), the number of people in Birmingham with CD would be approximately 2990. Using the online sample size calculator www.calculator.net, a confidence level of 95% was used to measure how accurately the sample size would represent the intended population i.e., 95% confident that the sample size would be representative. The population size was 2990 and the online calculator suggested a sample proportion of 50%. With these parameters sample size was calculated as n=341. Ideally, participants in a future study would be drawn from across the city to adequately represent the Birmingham population. A stratified sample would be required to ensure an appropriately ethnically diverse sample.

3.8 Statistical Methods

As per CTU direction, the protocol for the vitamin D screening study was contained within the overall D-CODE feasibility clinical trial protocol. All analyses for the screening study were pre-specified in a CTU statistical analysis plan together with analyses for the D-CODE feasibility study. Analyses were performed using SAS Institute Inc 2019, version 9.4 or later by CTU statisticians. To ensure data integrity and accurate analysis, the CTU recommended that no additional or separate analysis of data should be reported beyond that determined by the CTU in the statistical

analysis plan (Yuan et al., 2019, Gamble et al., 2017). Therefore, JF was unable to participate in any analysis of data with this role reserved for the CTU statisticians.

The number of patients evaluated for inclusion in the study, and the numbers eligible but not approached for consent, ineligible, not consented, and consented and recruited to the screening study were summarised. Without a formal power calculation, it was not possible to estimate any population parameters or do any statistical testing (section 3.7). Therefore, the main outcome measures including baseline characteristics were presented using descriptive summary statistics (Fletcher et al., 2021a), including frequencies, percentages, mean, median and interquartile ranges. The overall prevalence of vitamin D deficiency, defined as 25(OH)D <50nmol/L, was determined and additionally reported separately for each month.

3.9 Results

A total of 150 participants were successfully recruited giving a consent rate of 90.4% (Figure 3-1 and Table 3-2).

Table 3-2 Participant recruitment

Parameter	n (%)
Total patients screened	171
Ineligible	2 (1.71)
Not approached for consent	3 (1.75)
Consent not obtained	16 (9.36)
Recruited	150 (87.72)
Consent rate %	90.36

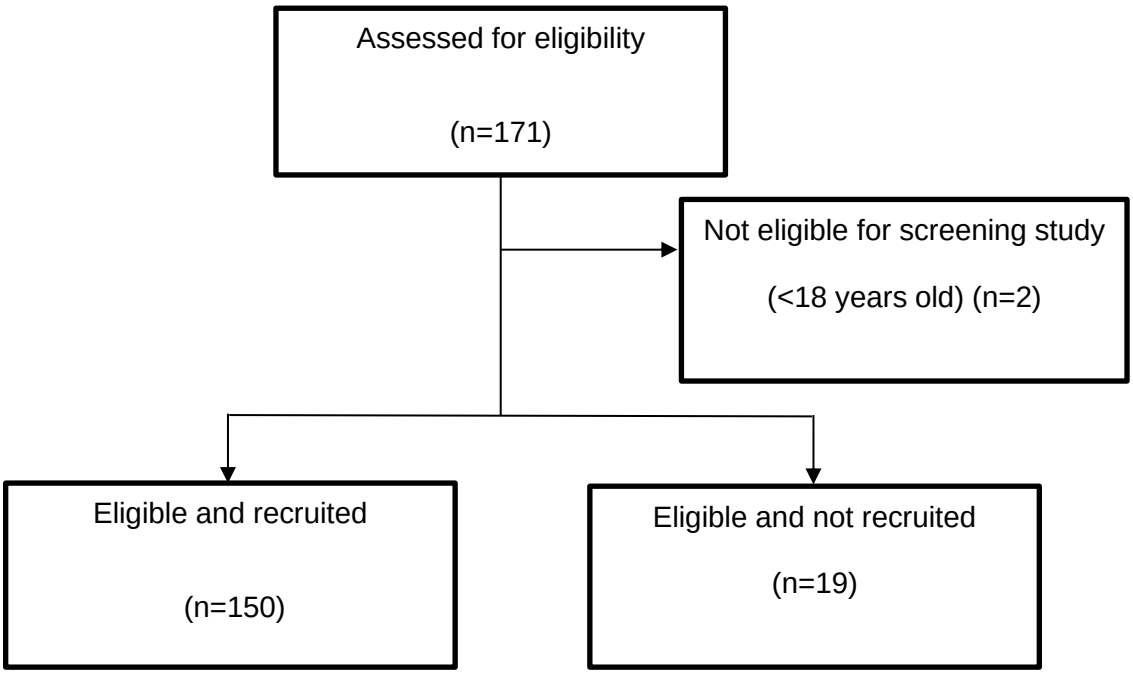


Figure 3-1 CONSORT flow diagram

Reasons for non-recruitment of eligible patients are detailed in Table 3-3, with the main reason for non-recruitment being participants who did not want to take part in research (n=6, 37.5%).

Table 3-3 Reasons for non-recruitment of eligible patients to screening study

Reasons for non-recruitment	n = 19
Not approached for consent	**3**
Reasons: n (%)	
Doctor did not want patient screened	1 (33.3)
Doctor felt patient too unwell	1 (33.3)
Doctor thought it was not clinically appropriate	1 (33.3)
Consent not obtained	**16**
Reasons: n (%)	
Does not want to take part in research	6 (37.5)
Unwilling to provide a reason	3 (18.8)
Too busy	3 (18.8)
Does not wish to have a blood test	2 (12.5)
Feeling too overwhelmed	1 (6.3)
Could not wait to be seen	1 (6.3)

Participant characteristics are detailed in Table 3-4. There is an even distribution between males and females, the majority of whom were from a White British background (n = 116, 77.3 %). Of 150 recruited participants, 31 (20.7%) were receiving a vitamin D supplement prescribed by a healthcare professional while 49 (32.7%) reported that they were taking an over-the-counter vitamin D containing supplement including fish oils and multivitamins. A total of 22 (14.7%) reported that they were current smokers. The patient's perception of their Crohn's disease status was reported as in remission for 36 (24 %) and active (receiving treatment) for 114 (76 %). Active included those whose symptoms were being controlled with medication.

Table 3-4 Participant characteristics

Characteristic	**n = 150**
Sex at birth, n (%)	
Female	80 (53.3)
Male	70 (46.7)
Age (years)	
Mean (SD)	42.7 (16.7)
Median (IQR)	39 (28-56)
Range	18-81
Ethnicity n (%)	
White English/Welsh/Scottish/Northern Irish/British	116 (77.3)
Indian	9 (6)
Pakistani	7 (4.7)
Any other Asian background	5 (3.3)
Any other White background	3 (2)
Any other Black/African/Caribbean background	3 (2)
Bangladeshi	2 (1.3)
Caribbean	2 (1.3)
White and Black Caribbean	2 (1.3)
African	1 (0.7)

Prevalence of vitamin 25(OH)D <50nmol/L was 53.3% (Table 3-5). There are missing data for just one participant where the sample was successfully collected, but a laboratory error occurred during analysis. This gives a 99.3% success rate with the collection and analysis of the DBS sample.

Table 3-5 Participant Vitamin D Levels

Vitamin D level as 25(OH)D	nmol/L
Mean (SD)	48.3 (25)
Median (IQR)	46 (31-62)
Range	11-185
Missing data	1 (0.7%)
	Number of patients
<25nmol/L	27 (18%)
25-<50nmol/L	53 (35.3%)
≥50nmol/L	70 (46.7%)

Table 3-6 details the month that vitamin D levels were measured and shows the highest prevalence of deficiency during November and December. It is unlikely that prevalence of vitamin D deficiency would reduce in January, and this figure is likely to indicate fluctuation within a small sample size. It is likely that prevalence of deficiency would be greatest in February and March towards the end of winter, however, screening did not extend into these months.

Table 3-6 Participant vitamin D levels and prevalence of deficiency by month

Month 25OHD measured	Number of patients each month	Number of patients with vitamin D deficiency*	Prevalence (%)
September '19	12	3	25
October '19	33	13	39.4
November '19	23	11	47.8
December '19	12	8	66.7
January '20	17	9	52.9
November '20	13	9	69.2
December '20	40	27	67.5
Total	**150**	**80**	**53.3**

* 25OHD <50nmol/L

In terms of reported sun exposure, most participants (n = 122, 81.3%) had not visited a warm sunny country outside of the UK during the three months prior to the study. The type of clothing the participants were most likely to wear in the sunshine is shown in Table 3-7. Most participants (n=91, 60.7%) reported they were most likely to wear shorts and a short- sleeved top. In terms of consumption of vitamin D containing foods, most participants (n=72, 48%) reported that they never/rarely consumed oily fish. However, 67 (44.7 %) consumed 1-2 portions of oily fish per week. The most consumed food was 1-2 portions per week of red meat (n=71, 47.3 %). Figure 3-2 shows weekly frequency of consumption of vitamin D containing foods. Data

collection was almost entirely complete, with only one participant failing to give a response to one food type (consumption of eggs).

Table 3-7 Patient reported sun exposure and skin type

Reported sun exposure	n (%)
Has the patient visited a warm/sunny country in the preceding three months?	
Yes	27 (18)
No	122 (81.3)
Missing data	1 (0.7)
In the sunshine is the patient most likely to wear…	
Shorts and a short-sleeve top	91 (60.7)
Long trousers/skirt and a short-sleeve top	31 (20.7)
Keep arms and legs covered	22 (14.7)
Keep whole body completely covered	6 (4)
If the patient is exposed to sunshine does their skin normally…	
tan or darken easily?	64 (42.7)
go red then tan?	49 (32.7)
burn?	36 (24)
Missing data	1 (0.7)
Would the patient normally use a sun lotion with sun protection factor (SPF) if they are exposed to sunshine?	
Yes	120 (80)
No	30 (20)
What SPF* would they normally use?	
Mean (SD)	38.2 (12.9)
Median (IQR)	45 (30-50)
Range	5-50
Unknown	38 (25.3 %)

*Although shown as continuous data in this analysis, SPF could also be reported as categorical data

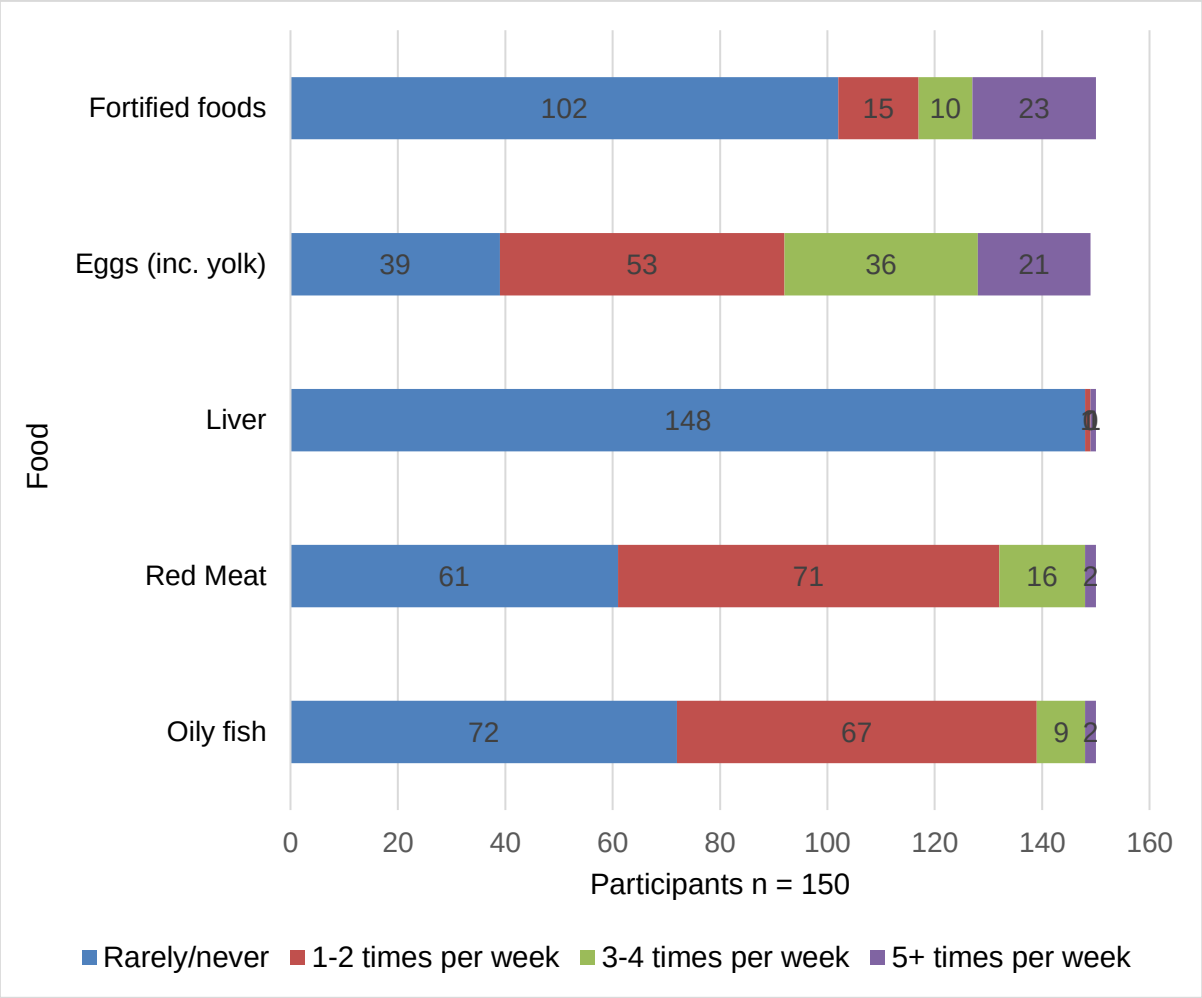


Figure 3-2 Participant reported weekly consumption of vitamin D containing foods. The majority of participants did not consume any oily fish, fortified foods or liver at all. The food most likely to be consumed 1-2 times per week was red meat followed by oily fish. Very few participants reported consuming any of the identified foods more than 1-2 times per week.

(Fletcher et al., 2023)

3.10 Discussion

At 53.3% the overall, primarily winter, prevalence of vitamin D deficiency found in this study is consistent with previously published, Northern European studies (Caviezel et al., 2017, Frigstad et al., 2017, Mccarthy et al., 2005). Target recruitment for QEHB was exceeded, with a total of 150 participants recruited and a greater than 90%

consent rate. Given the severe impact of the COVID-19 pandemic on research activity, this is a significant achievement (Fletcher et al., 2023).

3.10.1 Seasonal Variations

In the current study seasonal variations in vitamin D serum levels are demonstrated (Table 3-6), where prevalence of vitamin D deficiency was lowest at the end of summer, i.e., September in the UK, and then began to rise with the highest prevalence seen during November and December. Similar seasonal variations have been reported in other IBD studies (Bours et al., 2011, Janssen et al., 2019). Prevalence of deficiency was descriptively higher in November/December 2020 during the COVID-19 pandemic, compared with the same months in 2019 pre-pandemic. The first COVID-19 lockdown in the UK mandated the population to stay at home except to go out to buy food or for exercise once per day, and for non-essential shops and businesses to close. These restrictions are similar to those imposed in Italy from February 2020. Although it could be suggested that the impact of national lockdown during the pandemic influenced vitamin D levels, a large public health study in Italy found that there was little difference (Lippi et al., 2021). With similar restrictions on outdoor activity, the findings of this Italian study are likely to be broadly applicable to the UK population.

3.10.2 Dried Blood Spot Samples

In this study the use of the dried blood spot (DBS) test for collecting vitamin D samples was successful and well tolerated by participants, with all collected samples valid and received by the laboratory. The analysing laboratory reported an internal issue in the analysis of one sample, therefore, there was a >99% analysis success rate. DBS for vitamin D analysis has been shown to be as reliable as serum/plasma

sampling (Heath et al., 2014, Man et al., 2019, Zakaria et al., 2020) and is less invasive than venepuncture. DBS for vitamin D sampling has been used successfully in other research settings including in neonates (Smith et al., 2017, Mathew et al., 2019, Handel et al., 2017) and large nutritional studies (Hoeller et al., 2016, Livingstone et al., 2017)

The City Assays DBS kit is designed as a home test to the public, however, in the current study the PPI group advised that there would be better compliance if the DBS were administered by JF to build trust and confidence with participants (Fletcher et al., 2021c). A recent study investigating strategies to increase diversity in clinical trial recruitment found that mistrust of either the researcher or research process itself were key barriers to recruitment (Clark et al., 2019) . Given that some participants were later approached for inclusion in the feasibility study, it was hoped that building a trusting relationship initially would aid recruitment in the feasibility clinical trial. The PPI group were also concerned about the validity of DBS samples if participants did not follow the instructions correctly. Self-testing DBS for vitamin D sampling has previously been shown to achieve a 70% compliance rate (Sakhi et al., 2015). In a large epidemiological breast cancer study in Norway, 4597 participants received a DBS kit in the post for vitamin D sampling and a saliva sampling kit for carotenoids. In total 3263 samples were returned of which 225 were invalid. Of the returned samples there was a 93% validity rate (Sakhi et al., 2015). This would suggest that in a larger IBD observational study it would be feasible to use DBS as a participant self-administered test, thus widening the scope for inclusion and potential number of participants.

3.10.3 Food Frequency

A food frequency questionnaire (FFQ) format has the advantage of being a quick and easy method of data collection for participants and researchers. Nevertheless, there is debate regarding the value of FFQ compared to other methods of data collection, such as diet recall (Shim et al., 2014). In the current study, the FFQ format was successful with only one participant failing to provide a response to one food type. There are validated FFQs designed for the use with IBD patients, such as the Groningen IBD Nutritional Questionnaire GNIQ-FFQ (Peters et al., 2019). However, the focus of the current study was specifically intake of vitamin D containing foods, hence, the GNIQ-FFQ was too generic for the purposes of this study. Instead, usual weekly intake of the key vitamin D containing foods, as identified by NHS recommendation, were explored in this screening study.

Of the foods described, oily fish is known to be the best source of vitamin D however, few participants consumed one to two portions per week of oily fish recommended by the NHS (2018). Red meat contains lesser amounts of vitamin D but in the general population is an important source of vitamin D due to the large quantities often consumed. The current study found that just 47.3% of participants consumed one to two portions of red meat per week and 35.3% consumed one to two portions of eggs including the yolk. Previous studies have shown no correlation between dietary intake and 25(OH)D levels (Gilman et al., 2006). Nevertheless, the findings in the current study suggest that patients with CD are unlikely to maintain their vitamin D levels, or improve their vitamin D levels, from dietary sources. These findings are consistent with other studies that have shown limited dietary intake in some patients with IBD.

In the University of Manitoba IBD Cohort Study, 126 patients with IBD (CD 84, UC 42) completed a four-day diet history, including a weekend day, for nutritional assessment. Anthropometric and biochemical measures were also taken. Of those with CD, 45.8% had 25(OH)D <50nmol/L. A highly significant correlation (r = 0.41, p = 0. 0004) between dietary intake of vitamin D and serum 25(OH)D levels was found, with 38% of those with CD consuming inadequate amounts of dietary vitamin D (Vagianos et al., 2007).

A later study by Vagianos et al., (2016) considered dietary intake of IBD patients compared to healthy controls. Although, the data is not stratified for vitamin D containing foods specifically, based on the four-day history, the authors have given an indication of average weekly intake of key foods. Fish was consumed once per week (not specified as oily or not), red meat 2.8 and eggs 2.0 times per week. These findings are consistent with the intake reported in the current study. However, the Vagianos study was in IBD patients generally and not those with CD specifically.

Kuwabara et al., (2009) recorded a one-day diet history in 15 patients with CD in Japan and analysed the data for macro and micronutrient content. According to the one-day history vitamin D intake was adequate despite all CD patients having serum 25(OH)D levels <50nmol/L. This discrepancy may be due to malabsorption of vitamin D that is found even in patients with quiescent CD (Farraye et al., 2011). Furthermore, there are limitations with collecting only a one-day diet history, where daily dietary intake is likely to fluctuate.

In a cohort study (CD 173, UC107, healthy controls 42) investigating the correlation between dietary intake and gut microbiota, Weng et al., (2019) noted a reduced daily

intake of fish in patients with IBD compared to healthy controls (CD 21.4g/day ± 42.9, healthy controls 57.1g/day ± 71.8). The NHS describe a portion of oily fish as 140g and recommend consumption of one portion per week (National Health Service, 2018). The population in China, therefore, appear to consume much larger quantities of oily fish than the recommended amount for the UK population. Weng et al., observed an increased intake of eggs in those with CD (CD 25.7 g/day ± 36.6, healthy controls 17.7g/day ± 37.1). Mean vitamin D intake in patients with CD was 1.8µg ±4.2 per day, compared to 2.1±3.75 in UC and 0.9±1.4 in healthy controls. In this study, Weng et al., used the 2010 Chinese Residents of Nutrition and Health Status Monitoring Semi-Quantitative Food Questionnaire to collect dietary data with a one-year recall period. This is an exceptionally long recall period for dietary intake and thus, it is unclear how accurate the data is. Nevertheless, it does provide an indication of likely intake.

3.10.4 Sun exposure and Sun Protection Factor

The current study showed that most patients tanned easily and exposed large areas of skin to sunlight with SPF cover. The use of a high SPF is in keeping with general skin cancer prevention advice in patients with IBD and the public. While a recent review concluded that there was no association between the use of SPF and vitamin D levels (Neale et al., 2019), the authors recognise that reviewed studies overall did not include the real-life use of high SPF products recommended in the prevention of skin cancer. An early randomised controlled trial carried out in Australia, compared SPF17 with placebo in 113 adults aged over 40 years (Marks et al., 1995). No significant difference was found in 25(OH)D levels between the two groups (Marks et al., 1995). An experimental study using SPF 50+ and narrow band UVB exposure

showed that cutaneous production of vitamin D was reduced by 83-92.5% (Libon et al., 2017). However, serum vitamin D levels were only reduced by 7.7-13.2% (Libon et al., 2017). It is not possible to demonstrate any correlation between sun exposure and vitamin D levels in this screening study due to the limited statistical analysis of data carried out. Nevertheless, the use of increased sun exposure to manage vitamin D levels in patients with CD seems unfeasible given the significant increased risk of all types of skin cancer in this group of patients.

3.10.5 Smoking

Smoking has been shown to have an adverse effect on CD related clinical outcomes (To et al., 2016, Navarro Correal et al., 2021), therefore, it is encouraging that only 14.7% of participants in the current study were smokers. This may be partly because of routine clinical advice provided to patients regarding the risk of smoking exacerbating disease activity. Therefore, smoking is unlikely to be a significant contributing factor to vitamin D deficiency in the study participants overall.

3.10.6 Ethnicity

It is well recognised that CD is more prevalent among White populations (Barnes et al., 2021a, Barnes et al., 2021b). Nevertheless, studies have found that non-White people with and without IBD are more likely to have lower serum 25(OH)D levels than White people (Chatu et al., 2013, Fu et al., 2012, Kift et al., 2013). No conclusions can be drawn from the current study regarding the effect of ethnicity on vitamin D levels. Although there is some ethnic diversity within the study, with only 20% of participants being from a non-White background this is not representative of the overall Birmingham population (see section 3.10.8). However, it is likely that this is

representative of the population served by QEHB. Statistical analysis did not include analysis of vitamin D levels by ethnic background in the current screening study.

3.10.7 Crohn's Disease Status

Most participants (76%) reported that their CD was either active or they were receiving treatment to control it. This was a subjective assessment from the patient's perspective and so there is likely to be variability between participant reports. Although active CD has been shown to correlate with low serum levels of vitamin D (Jørgensen et al., 2013), this relationship was not explored within the analysis of the current study. However, there is growing debate suggesting that low levels of 25(OH)D are in fact a consequence of the inflammatory process (Mangin et al., 2014), such as that seen in active CD, rather than a cause. A study of 30 patients who underwent a knee operation found that vitamin D levels reduced immediately post operatively, where inflammatory markers such as CRP increased (Waldron et al., 2013). Patients had varying levels of vitamin D status preoperatively, adequacy (>50 nmol/l) 53%, insufficiency (30–50 nmol/l) 17% and deficiency (<29 nmol/l) 30%. The authors suggest that the overall decline in vitamin D levels was a response to the postoperative inflammatory response. This is an important aspect to take in to consideration when interpreting vitamin D levels in the presence of active inflammation.

3.10.8 Patient and Public Involvement

Several challenges were encountered in enabling effective PPI to be embedded within the study. Challenges included pre-award funding for PPI activity, identifying and engaging with patients to become PPI group members and managing ongoing interactions. In terms of the strategy for identifying PPI collaborators, a direct

approach was successful. The patients approached had never considered collaborating in research before and so would not have been reached via open forums or other PPI groups. As a nurse JF was fortunate to have existing therapeutic relationships with patients (Ozaras and Abaan, 2018, Strandås and Bondas, 2018) that formed the foundation of relationships with the PPI group. It can be suggested that familiarity gave patients confidence to participate and express their opinions freely. However, this relationship can contribute to a sense of obligation on the part of the patient. Postal contact rather than a face-to-face invitation and the voluntary nature of the invitation was important in mitigating this. This allowed patients plenty of time to consider the invitation and gave them the option to choose to respond or not (Fletcher et al., 2021c).

A weakness in the strategy for identifying PPI members was the lack of diversity in the PPI group and it is possible that this may have impacted on the recruitment strategy for those from diverse ethnic backgrounds. The PPI group was not representative of the study population in several respects. Firstly, the lack of ethnic diversity was regrettable when there are ethnic differences in the prevalence of vitamin D deficiency (Chatu et al., 2013) and an increasing prevalence of IBD in Black and minority ethnic groups (Alexakis et al., 2015). PPI involving community members has been shown to be important in engaging with people from ethnic minority backgrounds effectively (Farooqi et al., 2022, Dawson et al., 2018).Secondly, Crohn's Disease may affect people of all ages, but the median age of diagnosis is 29.5 years (Shivashankar et al., 2017); the PPI group members were older than this. Thirdly, the PPI group members were identified from a cohort of patients with

intestinal failure, a particularly severe or complex form of the disease, where this is unlikely to be the experience of all patients with IBD (Globaldata, 2017).

In the future, development of a more diverse PPI group would be sought by working with other clinical teams and stakeholders. Direct invitation was a successful strategy in recruiting group members for the current study. Liaising with IBD teams from across the city to identify other groups of patients to invite would help ensure a more culturally diverse group from different socioeconomic backgrounds. Different, culturally sensitive strategies are required to recruit hard to reach groups and local teams are likely to be best placed to guide this. In a study exploring experiences of women living with and cooking for family members with Type 2 diabetes, Redwood et al., (2012) found that South Asian women were an under-represented but important group. Contact was made with registered voluntary organisations and community groups through their gatekeeper. The initial approach was on the woman's home territory, by a person they were familiar with who had received instruction and information from the research team. This was a successful strategy with 120 women participating in the study over a 12-month period.

A systematic review of 22 articles regarding involvement of disabled children and young people in PPI, found a several different approaches used (Bailey et al., 2015). These included liaison with partner organisations such as youth groups advertising in schools and hospitals and the use of social media. In engaging with this group practical considerations included ensuring meeting venues were accessible, ensuring communication aids were available where required and ensuring engagement activities were flexible to meet the needs of differing abilities.

3.11 Limitations and Generalisability

The primary purpose of this study was to establish the prevalence of vitamin D deficiency in the Birmingham UK cohort of patients with CD. This would support a rationale to continue exploration of vitamin D deficiency in this cohort and establish feasibility of recruitment to a vitamin D supplementation clinical trial. The difficulties in identifying suitable space with each NHS site from which to recruit, and the advent of the COVID-19 pandemic, limited recruitment. While the target number was achieved from a single site, the ethnic diversity of the sample did not reflect the proportions of different ethnic groups in the city. A future study involving cross-city collaboration with other sites would provide a better indication of the effect of ethnicity on 25(OH)D serum levels in this group.

A further limitation is the lack of a sample size calculation preventing comparative statistical analysis and identification of any correlation between vitamin D deficiency and risk factors to be planned within the statistical analysis plan. Analysis such as regression analysis and correlation co-efficient would have been useful in establishing relationships. Absence of these statistics made it very difficult to get the study published, as reviewers generally requested that these were added. Even though changes to the statistical analysis plan were requested before analysis began, the CTU were not willing to incorporate any statistical tests. This would be an important point to address in the planning of any future study.

3.12 Interpretation

Vitamin D deficiency defined as 25(OH)D <50nmol/L is prevalent in Birmingham in patients with CD. However, this level relates to the amount of vitamin D required to achieve beneficial skeletal effects. There is continued debate regarding the optimal

level of vitamin D required in IBD to achieve non-skeletal benefits. Evidence suggests that 25(OH)D levels of 75-100nmol/L are desirable to achieve non-skeletal benefits in patients with IBD (Nielsen et al., 2019). However, this level has not yet been determined within clinical practice.

In a randomised, placebo- controlled trial of 40 patients with CD, high dose vitamin D (200,000IU) was administered weekly over a 7-week period (Bendix et al., 2020). Results showed that high-dose vitamin D given as monotherapy for 7 weeks decreased mucosal IL-17A expression by 55% (median ratio 0.45 (95%CI: 0.22–0.95)) (p = 0.04). Vitamin D serum level after treatment was median 218nmol/L. A 12-month follow up study of the participants who continued infliximab treatment (n=35) showed that patients maintained their 25(OH)D levels >75nmol/L until week 31 (Bendix et al., 2021). During this time, no dose escalation in infliximab treatment was required and disease inflammatory markers were lower than in the placebo group. When 25(OH)D levels dropped below 75nmol/L, three participants in the vitamin D group required dose escalation compared to 13 in the placebo group. These results demonstrate the clinical benefits of maintaining 25(OH)D >75nmol/L in patients with CD receiving infliximab. Speculatively, if a higher vitamin D level was adopted in patients with CD, the prevalence of deficiency is likely to be higher than currently demonstrated with the lower cut off level.

3.13 Conclusion

In conclusion, this study demonstrated that patients with CD in Birmingham are at high risk of vitamin D deficiency as defined by 25(OH)D serum levels <50nmol/L typically used as the ‘cut off’ level in clinical practice. The prevalence of vitamin D

deficiency in this cohort is consistent with findings of previously published studies, including the influence of season on 25(OH)D serum levels. Patients with CD in the UK are unlikely to increase or maintain their vitamin D serum levels from intake of dietary sources or over-the-counter vitamin supplements. Therefore, the proposed use of dietary advice and sun exposure suggested by clinicians in the previously reported current practice survey (Fletcher et al., 2020) are at odds with the findings of this study. In this group, vitamin D supplementation may be required at higher doses than frequently found in over-the-counter preparations or within standard prescribing practice. RCTs are required to determine the most effective dose of vitamin D supplementation in this patient group.

4 Project C: D-CODE Feasibility Study for a vitamin D supplementation randomised controlled trial

Lead researcher: Jane Fletcher, Primary supervisor: Dr Amelia Swift, Co-supervisor: Professor Martin Hewison Clinical Supervisor: Dr Sheldon Cooper

4.1 Introduction

People with CD are at considerable risk of developing vitamin D deficiency due to several factors including ethnicity, diet, and other lifestyle factors. The previous observational screening study demonstrated that many UK people with CD are unlikely to maintain adequate vitamin D levels through their diet or sun exposure, particularly during the winter months in the UK (Fletcher et al., 2023). Therefore, the use of vitamin D supplementation is required to ensure sufficient vitamin D levels in this group. The earlier current practice survey (Fletcher et al., 2020) showed that Gastroenterologists felt they needed better evidence and clearer guidance in the identification and management of vitamin D deficiency in this group. It is believed that RCTs offer the most definitive evidence of efficacy and influence on national guidance.

RCTs looking at non-skeletal effects of vitamin D supplementation in a variety of disease states have generally been inconclusive. This is due, in part, to some studies focusing on the protective effects of vitamin D in preventing a disease, whilst other studies have focused on possible beneficial effects of vitamin D as a therapy for those who already have the disease. It is important to note that many studies do not specifically recruit those that are vitamin D deficient at baseline (Kmietowicz, 2014). A study of the effect of vitamin D and calcium supplementation on recurrence of colorectal adenomas showed no significant difference between treatment and

placebo (Baron et al., 2015). However, in this study of 2259 participants given 1000IU vitamin D or placebo, 25(OH)D levels ranged from >30nmol to <225nmol/l suggesting that some participants were not vitamin D deficient. A recent RCT investigated the effect of three different doses of vitamin D supplementation (12,000IU, 24,000IU, 48,000IU per month) on BMD in 379 people aged >70 years. No significant difference was seen in BMD when the doses of vitamin D supplementation were compared. However, mean 25(OH)D levels at baseline were 40nmol/L, again suggesting that there was heterogeneity in levels of deficiency among participants, with some participants not having vitamin D deficiency (Aspray et al., 2019).

Those who are vitamin D deficient are most likely to benefit from supplementation (Bouillon et al., 2022) and there is a convincing argument for only including vitamin D deficient patients in supplementation trials (Scragg, 2018, Boucher, 2020). A large, population-based mortality cohort study in adults (n = 9949) from Germany, determined that targeted supplementation of people with vitamin D <50nmol/L was likely to have higher power in studies than untargeted supplementation (Brenner et al., 2017). Thus, including participants without an identified vitamin D deficiency at baseline is likely to skew study results unfavourably. RCTs that purposely include only those people with an identified vitamin D deficiency are needed to investigate the effects of supplementation more accurately. As discussed, there is debate regarding the specific serum level of 25(OH)D that suggests deficiency, particularly in patients with CD and other forms of IBD. Nevertheless, a cut off level for vitamin D deficiency <50nmol/L 25(OH)D seems sensible and clinically relevant for the purposes of investigation (section 1.3.2).

4.2 IBD Studies

In IBD specifically there are several RCTs looking at the non-skeletal effects of vitamin D, investigating a variety of aspects of the disease and patient outcomes, and with varying doses of vitamin D used. Dadaei et al., (2015) investigated TNF-α levels and Crohn's Disease Activity Index (CDAI) score in response to 50,000IU/week vitamin D for 12 weeks or none in 108 IBD patients. At baseline mean 25(OH)D levels were 38.7 nmol/L and 54 nmol/L respectively. Patients with a 25(OH)D >75nmol/L were specifically excluded. TNF-α serum level reduced but was not statistically significant (p= 0.07). It is unclear what effect vitamin D supplementation had on the CDAI score in this study and it is not reported if this was a blinded or unblinded study.

In a small, double-blind study of 27 patients with CD in remission, Raftery et al., (2015) investigated intestinal permeability, antimicrobial peptides, disease activity markers including CDAI in response to 2000IU/ day vitamin D for 12 weeks, or control. Mean 25(OH)D levels at baseline were 69.2 nmol/L in the treatment and 51.8 nmol/L in the control group. There was no change in CDAI or disease activity markers, intestinal permeability did not improve, and antimicrobial peptides were only improved at vitamin D levels >100nmol/L, suggesting the need for a higher cut off point in CD patients. A double-blind pilot study of 34 CD patients in remission, investigating disease relapse and patient anxiety/depression scores, randomised patients to 1000IU/day or 10,000IU/day vitamin D for 12 months (Narula et al., 2017). Mean 25(OH)D levels at baseline were 71.3 nmol/L and 73.5 nmol/L respectively. There was no statistically significant difference in disease relapse rates or anxiety/depression scores at the end of the study. However, as a pilot study it was

not powered to detect a difference between treatment arms. The effect of 25,000IU/week vitamin D compared to placebo, for 26 weeks, on recurrence of CD after ileocolonic surgical resection was investigated in a double-blinded RCT involving 143 patients with CD (De Bruyn et al., 2020). Median 25(OH)D levels at baseline were 42nmol/L and 43nmol/L respectively. Endoscopic recurrence, CDAI and quality of life scores were key outcomes. However, authors report that there was no difference in clinical recurrence between the two groups, although quality of life scores increased slightly in the treatment group (p=0.07).

A small double-blind study of 18 patients with UC, randomised to receive either 2000IU/day or 4000IU/day vitamin D for 12 weeks, investigated disease activity and quality of life (Mathur et al., 2017). All patients were vitamin D deficient with mean baseline levels of 42.5 nmol/L and 35.5 nmol/L respectively. In this study there was an improvement in quality-of-life scores with no statistical difference between the two groups. In a larger double-blind study of 50 patients with UC, randomised to 1000IU/day or 2000 IU/day of vitamin D for 12 weeks, the quality-of-life mean score significantly increased in high dose group compared to the low dose group ($p = 0.001$) (Karimi et al., 2019). In addition, disease activity scores improved in both groups (-2.58 ± 2.16 and -0.9 ± 0.3 in high dose and low dose respectively). Baseline 25(OH)D levels were 60nmol/L low dose group and 54.5nmol/L in the high dose group.

The studies described all report the greatest increases in 25(OH)D levels in patients receiving the higher doses of vitamin D. However, levels increased in all patients

given vitamin D supplements regardless of the dose. The heterogeneity of the studies in terms of patient population, outcomes, vitamin D doses and baseline 25(OH)D levels make it difficult to draw any useful conclusions from them. The inclusion of Patient Reported Outcome Measures (PROMs) in RCTs is becoming increasingly important to ensure patient-centred care (Calvert et al., 2013) and to determine efficacy of treatment from the patient's perspective. It is reported that PROMS, or a measure of quality of life, were included in all the IBD studies mentioned. However, there was no consistency between the choice of PROM or rationale for those chosen.

Hence, to try to address some of the inconsistencies seen in some studies, D-CODE was designed to include only patients with identified vitamin D deficiency defined as serum levels of <50nmol/L 25(OH)D and using validated PROMs as the primary outcome. It is important to test trial processes and design to determine feasibility prior to launching a full scale RCT (Craig et al., 2008). Feasibility studies have been shown to be useful at reducing waste in research funding by assessing if a full trial is likely to be successful (Morgan et al., 2018). The D-CODE feasibility study was the first important step in establishing D-CODE as a full RCT for the future. The CONSORT 2010 Statement has been used in the reporting of this study (Schulz et al., 2010).

4.3 Aims and Outcomes

***Primary aim*:** To assess the feasibility of conducting a national, multi-site Randomised Controlled Trial (RCT) in adult patients with CD and vitamin D deficiency, to determine whether vitamin D supplementation improves clinical markers, symptoms of disease and patient reported health related quality of life.

4.3.1 Feasibility Outcomes and Measures

1. Consent rate - 50% of eligible patients can be consented.
2. Compliance rate - 80% participant compliance with the intervention.
3. Retention rate – 24-week retention and follow up in 80% of participants.
4. Completion of trial processes in 80% of participants
5. Adverse events - Absence of causative AEs in 80% of participants

4.3.2 Efficacy Outcomes

The feasibility of implementing the following measures in the future RCT were assessed:

Primary outcome: Improvement in the score of a disease specific patient reported outcome measure – Inflammatory Bowel Disease Questionnaire (IBDQ -32) (Guyatt et al., 1989).

Secondary outcomes:

1. Improvement in the score of a generic health utility measure (EQ-5D-5L) (Euroqol Research Foundation, 2019)

2. Improvement in Crohn's Disease Activity Index Score (CDAI)(Best et al., 1976)

3. Increase in serum (25(OH)D

4. Activity of other vitamin D metabolites

5. Corrected calcium levels within normal limits

6. Parathyroid hormone levels within normal limits

7. Change in hepcidin levels in response to the vitamin D supplement

8. Presence of iron deficiency anaemia

9. Presence of inflammation

10. Improvement in faecal calprotectin levels indicating resolution of inflammation

Secondary Aim: To investigate the role of the researcher in a hybrid study with the researcher carrying out trial co-ordination.

4.4 Methods

4.4.1 Study Design

In the intervention phase D-CODE was a feasibility study for a phase IV, open label, multi-site, superiority RCT and was classified as a CTIMP for regulatory purposes. Participants with vitamin D-deficiency (<50nmol/L 25(OH)D) identified in the previously described, concurrent screening study were considered for inclusion in the vitamin D supplementation clinical trial. Participants were able to consent to participation anytime during the recruitment period to allow ample opportunity.

Participants were randomised to one of two parallel arms (A or B). The primary endpoint was an improvement in health-related quality of life and CD symptoms after 24 weeks of treatment for vitamin D deficiency. Arm A (the control group) received a low dose of vitamin D oral capsule 400IU daily for 24 weeks. Arm B (the intervention group) received a higher treatment dose of vitamin D oral capsule consisting of 3,200IU daily for 12 weeks followed by 800IU daily for 12 weeks. The D-CODE protocol was designed and in accordance with the SPIRIT statement (Chan et al., 2013) and published via open access (Fletcher et al., 2021a). The participant

pathway including all elements of the study is shown in Figure 4-1. The CTU recommended the additional baseline appointment to ensure all blood tests were re-checked to confirm eligibility prior to randomisation.

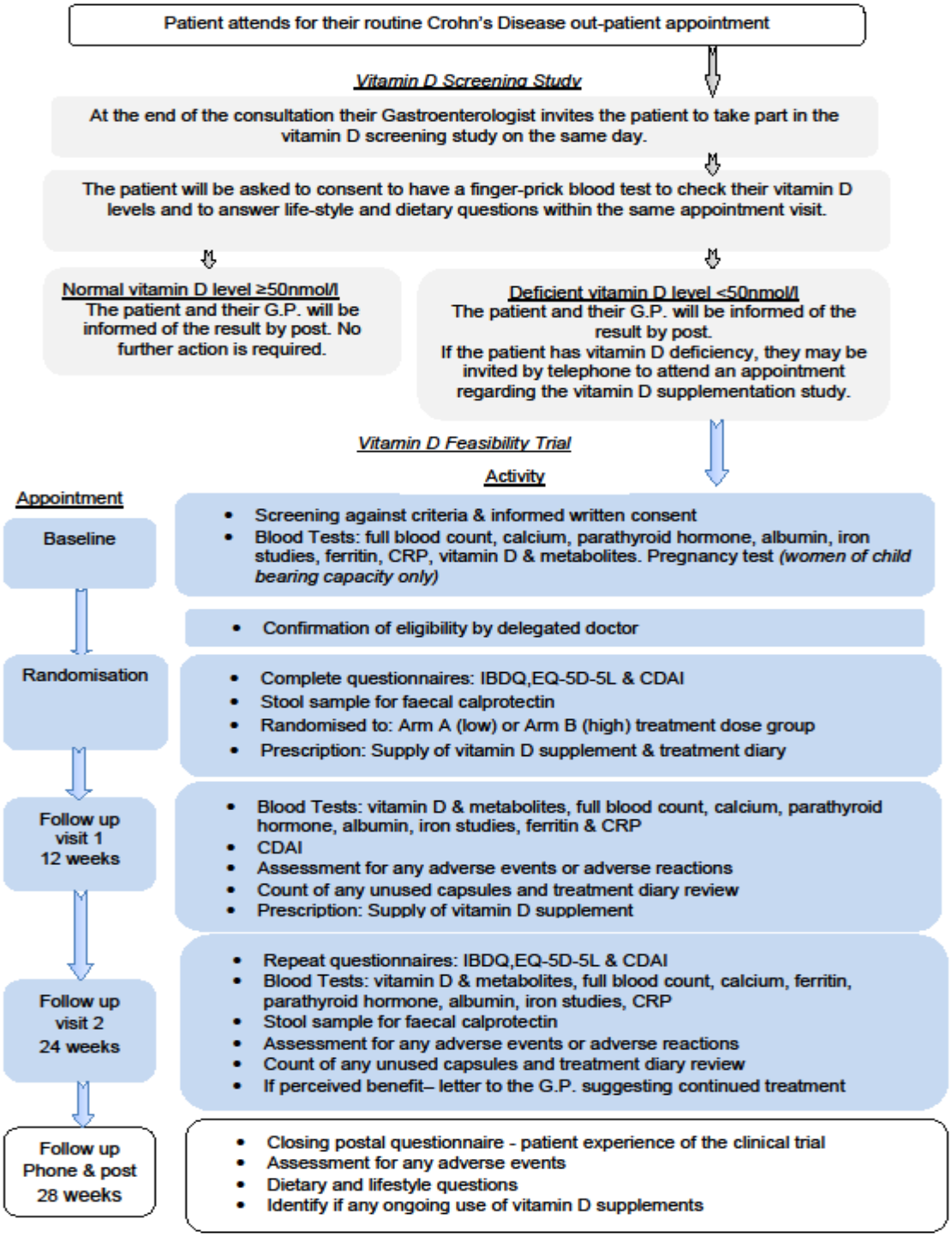


Figure 4-1 Participant pathway. Participants were identified from the screening study and randomised to 400IU, or 3,200/800IU vitamin D for 24 weeks. Biochemical measures and CDAI were taken at baseline, 12 and 24 weeks. Faecal calprotectin and PROMS were done at baseline and 24 weeks. There was a total of five study appointments, with a final questionnaire at 28 weeks and reassessment of diet and sun exposure.

According to good practice in clinical trials, the trial was registered with public trial registries. Registration numbers: EudraCT number 2018-003910-42, ClinicalTrials.gov identifier: NCT03718182 and ISRCTN number: 15717783. Ethical approval was via North East - Newcastle North Tyneside 2 Research Ethics Committee, Holland Drive, Newcastle Upon Tyne, NE2 4NQ, reference: 19/NE/0019. Regulatory approval was granted by the Medicines and Health Care Products Regulatory Agency (MHRA) and the Health Research Authority (HRA) (Appendix 4). Five protocol changes took place (Appendix 6). Patient information sheets and other study documents were updated as necessary and regulatory approvals gained for amendments.

4.4.2 Identification of a Clinical Trials Unit

The need to ensure national expertise in the development and delivery of high-quality, multi-centre clinical trials was first identified by the UK National Cancer Research Network, recognising the essential role that Clinical Trials Units (CTU) play. The CTU accreditation process was later extended to include non-cancer trials and trials units (Mcfadden et al., 2014). To date the UK Clinical Research Collaboration (UKCRC) (2019) reports 51 publicly funded CTUs registered on the CTU network. Although the role of a CTU may vary according to requirements of the trial and Sponsor, it often includes trial design, managing the conduct, data management, data analysis and publication of trials, spanning different diseases and settings (Hopkins et al., 2016). As D-CODE was a CTIMP, involvement of a CTU was essential to assure the funders and Sponsor that the trial would meet all necessary regulatory standards. CTU's are the monitors of clinical trials and are responsible for

ensuring the integrity of data, safety of participants and that the trial is being conducted according to the approved protocol (Love et al., 2020).

CTU's expect to be approached eight to twelve weeks in advance of any funding application to allow them adequate time to collaborate on the study design and determine what is required of the CTU. The CTU costs must then be included in the funding application. Although there may be a temptation to approach a CTU that is geographically convenient, it is important to note that many CTU's have specific expertise and research interests. Therefore, it is more appropriate to find a CTU that can work within the specific disease or speciality related to the research.

The initial research plan was discussed with the West Midlands Research Design Service (RDS) who suggested approaching a CTU and introduced JF to Birmingham Clinical Trials Unit (BCTU). BCTU agreed to review the proposal. Useful design suggestions were given, for example, using a multi-centred design. However, BCTU declined to support the trial and funding application as they expected the application would fail. The UKCRC register was then reviewed to identify other units to approach as follows:

a) Oxford Clinical Trials Research Unit - links with the Oxford Translational Gastroenterology Unit and so relevant to CD research
b) Leicester Clinical Trials Unit - gastrointestinal diseases were listed as one of their research interests and so relevant to CD research
c) Liverpool Clinical Trials Centre (LCTC) (formerly the Clinical Trials Research Centre)– experience in paediatric studies but they were open to other collaboration opportunities

Both Oxford and Leicester CTU's expressed an interest in the study proposal but both declined to support the study as they felt they could only support local fellowships. LCTC expressed an interest and after review of the research proposal by the CTU Director they agreed to support the study.

4.4.3 Setting

The vitamin D supplementation trial took place in the same clinical setting as the previously described vitamin D screening study. Although the trial was planned to include three sites, due to logistical issues at BHH and GHH, only QEHB site opened and recruited.

4.5 Participants

Participants were initially identified from the results of the vitamin D screening study (section 3.9). Those with total 25(OH)D levels <50nmol/l, and who had none of the listed exclusion criteria according to the medical information collected during the screening study, were contacted by telephone, and invited to a baseline appointment to discuss the vitamin D supplementation trial.

4.5.1 Eligibility Criteria

4.5.1.1 Inclusion

Those:

- With a confirmed diagnosis of CD
- Identified as vitamin D deficient 25(OH)D < 50 nmol/L in the screening study
- ≥ 18 years of age

- Receiving treatment for CD as per NICE guidance or those in remission but who continue to have hospital out-patient clinic appointments
- Provided written informed consent

4.5.1.2 Exclusion

Those:

- Taking over the counter vitamin D, multi-vitamin supplementation or fish oil and unwilling to stop this to participate in the feasibility trial, due to the risk of the additional vitamin D skewing study results or precipitating vitamin D toxicity
- Receiving any vitamin D supplementation prescribed by a healthcare professional, as it was deemed unethical to halt a medically prescribed treatment for the trial
- Receiving Bisphosphonates
- Receiving Digitalis or other cardiac glycosides
- Receiving Phenytoin
- Receiving Barbiturates
- Receiving Actinomycin
- Receiving Imidazole
- With known hyperparathyroidism
- With known sarcoidosis
- With known renal disease or kidney stones
- With known hypercalcaemia (corrected calcium ≥2.60 mmol/L)
- With known underlying liver disease

- With a known allergy to vitamin D supplements or any of the supplement excipients
- Due to the lack of safety data on the use of high dose vitamin D during pregnancy and breast feeding; women who were pregnant, breast feeding or trying to conceive at the time of recruitment. Women of child-bearing capacity who declined to have a pregnancy test where applicable and/or declined to take contraceptive measures during the intervention period.
- Due to the risk of unknown incompatibility between treatments, any patient had participated in another trial testing a medicinal product within 6 months preceding the screening study.

The vitamin D Summary of Produce Characteristics (SmPC) noted that concomitant treatment with Phenytoin or barbiturates can decrease the effect of vitamin D. The cytotoxic agent Actinomycin and Imidazole antifungal agents further interfere with vitamin D activity. Vitamin D may accentuate the effects of digitalis and other cardiac glycosides if given with calcium and vitamin D. Therefore, any patients receiving these medications were excluded. A few medical conditions were additionally identified in the SmPC requiring caution, therefore, patients with sarcoidosis, hypercalcaemia, liver, or renal disease were excluded. Those with known hyperparathyroidism were also excluded due to the difficulty of interpreting calcium biochemistry in this condition.

4.5.2 Consent

Patients who expressed an interest in joining the vitamin D supplementation trial were sent the participant information sheet in the post (see Appendix 9) to allow them adequate time to review the information prior to their baseline appointment.

Information was then discussed in more detail at the baseline appointment. Informed written consent was then gained in those who wished to proceed.

4.5.2.1 Altered recruitment and consent process due to COVID-19

During the period of reduced contact, due to COVID-19, routine outpatient appointments were suspended. Patients were sent the participant information and consent form in the post with a reply-paid envelope with the offer of a telephone or video call with JF to discuss the study and gain the patients consent to participate. Participants returned the signed consent form in the reply-paid envelope. On receipt of the signed consent form JF arranged necessary assessments. In addition, to reduce face-to-face contact, participants who were not attending hospital for a clinical visit were able to receive telephone or video research follow up consultations.

4.5.3 Confidentiality

Confidentiality was maintained by referring to participants via an eight-digit randomisation number and their date of birth on CRFs submitted to the CTU. Other confidentiality and data management arrangements have been described in previous sections (3.4.3 and 3.4.4).

4.6 Oversight Committees

In the UK, three key oversight groups, or committees, are required to ensure good clinical practice, safety of participants and robust data in clinical trials (Lane et al., 2020). These include a Trial Management Group (TMG), an Independent Data and Safety Monitoring Committee (IDSMC) and a Trial Steering Committee (TSC) (Vere, 1999). JF was responsible for convening these three committees in the role as trial manager.

4.6.1 Trial manager

Each clinical trial must have a trial manager, who would often by an employee of a CTU. Unusually, in D-CODE this role was carried out by JF to further expand research skills and knowledge (Appendix 11). The person in this role steers the trial and ensures that the required elements are present, and processes are completed. The trial manager leads on:

- Protocol development and content
- Participant information sheets and consent form development and content
- Convening trial oversight committees and drafting terms of reference
- Risk assessment development with the CTU team, investigators, and Sponsor
- Review of the risk assessment following any amendments
- Creating the Trial Master File contents list
- Creating the Individual Site File contents list
- Drafting the annual Research Ethics Report
- Writing the annual Development Safety Update Report for the Medicines and Health Care Products Regulatory Agency (MHRA)
- Ensuring all required documents and approvals were in place, completing the Greenlight Check list prior to study initiation
- Ensuring all required documents and approvals were in place for each site and completing the Site Greenlight Check list before any site was opened.
- End of trial reports to regulatory agencies and Sponsor

The trial manager is responsible for:

- Organising all Trial Management Group, Trial Steering Committee, Independent Data and Safety Monitoring and CTU Internal Team meetings, writing and circulating agenda and minutes
- Obtaining initial study regulatory approvals and all administration related to this (i.e., being aware of requirements for ethical and MHRA review)
- Trial registration and updating the registration as required.
- Managing amendments, notifying Sponsor, regulatory agencies, recording responses and disseminating approval, and all administration related to this
- Creating the Trial Master File and maintaining this with a complete history of the trial
- Creating the Individual site files for each site
- Carrying out site training visits including reporting of serious adverse events
- Ensuring pharmacy had supplies of IMP at the correct time
- Carrying out and recording the monthly IMP version check
- Creating the pharmacy file
- Ensuring all reports were submitted within regulatory timeframes
- Site closeout
- Study closeout
- Weekly supervisory meeting with the Senior Trial Manager
- Following and keeping up to date with all relevant CTU standard operating procedures and updates, information systems and training.
- Attending monthly CTU internal study team meetings.
- Providing monthly reports and updates as required by the senior management team at CTU from their trial managers.

- Responding to Quality Assurance queries

Within the trial manager role JF followed all CTU standard operating procedures related to these activities.

4.6.2 Trial Management Group

The TMG is responsible for the day to day running of a clinical trial and would often include the Chief Investigator for trial leadership, other clinical input and the trial team such as statistician, trial manager and data manager (Lane et al., 2020). Being a fellowship, the TMG for D-CODE included clinical and academic supervisors, the CTU trial team, the clinical trials pharmacist from QEHB and a Sponsor representative, in addition to the Expert by Experience – IBD PPI group. Although the frequency of meetings of a TMG may vary according to the individual trial, in D-CODE monthly meetings were planned to ensure regular discussion of any issues related to the trial, and to enable regular supervisory meetings. The first TMG meeting was convened September 2018 in preparation for study set up.

4.6.3 PPI involvement in Trial Management Group

A TMG is convened once a study has received funding and regulatory approvals, and preparations are underway for study set up. PPI members continued to be essential in the TMG in contributing to issues related to participant recruitment/retention and continued review of participant facing documents.

The first D-CODE TMG face-to-face meeting was held with all members of the research team and PPI group members. The PPI members noted that many agenda items were academic and felt that much of this was not relevant to them. Gray et al., (2000) noted that PPI members should be protected from the burden of excessive

information and demand on their time. In a review of PPI input within the OPUS project, Brown et al., (2018) found that PPI members reported they were sometimes overwhelmed by the volume of information they were sent and were unsure what they were supposed to do with it. They go on to recommend that there should be separate meetings for academic business, with specific meetings involving PPI where this is necessary and relevant to PPI members. For these reasons the TMG agreed with PPI members that they be invited to attend meetings where there was something specifically relevant to them. Within D-CODE PPI members were kept informed of key developments within the study either by email, post, or informal conversations.

4.6.4 Independent Data and Safety Monitoring Committee

The key role of the IDSMC in trial oversight is the monitoring of accumulating evidence/data related to benefit, toxicity, and safety of the intervention (Grant et al., 2005a) presented to them by the trial statistician. The IDSMC has an advisory role, reporting to the TSC (Conroy et al., 2017) and would usually be comprised of at least an independent Chair, clinician, and statistician (Damocles Goup, 2005).

In D-CODE, the independent Chair and clinician were invited from independent experts known to the clinical supervisor (SC). The Chair was known to have extensive research experience and the clinician was a Gastroenterologist with IBD clinical experience. The independent statistician was identified by the CTU statistician from a national network of statisticians who volunteer to collaborate in oversight committees. The first D-CODE IDSMC was convened in January 2019. Although frequency of meetings varies according to the clinical trial, the IDSMC would expect to meet at least annually. In D-CODE there were a total of five IDSMC meetings.

4.6.5 Trial Steering Committee

The role of the TSC is described by the Medical Research Council (MRC) as a committee of independent experts, providing advice to the TMG regarding the ongoing conduct of the trial (Vere, 1999) and acting as advocates for study participants (Daykin et al., 2016). The TSC usually meets after the IDSMC, to consider data that has been presented by the IDSMC and any recommendations to continue/modify/halt the study.

The independent members of the TSC are usually comprised of a Chair, statistician, a clinician, and PPI representation. In, addition key trial team members from the TMG are involved (Lane et al., 2020). A survey of 38 UK CTUs found that 71% of trials required a TSC to be involved in oversight. Of the trials that did not have a TSC reasons included that it was not required for a pilot/ feasibility study, the CTU had experience from previous trials in the area or the intervention had a well recorded safety profile (Conroy et al., 2015). It could be argued that even in a pilot/feasibility study the welfare of participants is a priority and therefore the involvement of a TSC should be mandatory.

The TSC Chair and clinician were invited from independent experts known to the clinical supervisor. Both the Chair and clinician were Gastroenterologists with IBD clinical experience and previous research experience. The independent statistician was invited by the CTU statistician from a national network of statisticians who volunteer to collaborate in oversight committees. In an interview survey of oversight in eight UK clinical trials, the role of PPI was described as the participants voice or advocate by both researchers and PPI representatives (Coulman et al., 2020). As with the Expert by Experience-IBD group, a similar direct approach was used to invite

three patients who had been service users for several years to collaborate in the TSC (Fletcher et al., 2021c). In this instance JF was keen to work with patients who had been service users for several years but who did not necessarily have IBD. Their wider experience of healthcare services was valuable in their role as patient advocates.

The NIHR funding review panel recommended that there should be two to three PPI representatives to ensure there would be a representative at all TSC meetings. All three patients who were invited to join the TSC accepted. From the three there was one retired, one employed and one unemployed, two were male and one was female, all from a White British background and none had been involved in research previously. Coulman et al., (2020) discuss the difficulty of finding 'the right people' for oversight committees, and there is debate regarding training required by PPI members for their contribution to be effective (Dudley et al., 2015). Nevertheless, the professionalisation of PPI members may lead them to be unrepresentative of the average participant (El Enany et al., 2013); when it is their expertise as health service users that brings value to their advocacy role (Fletcher et al., 2021c).

The first TSC meeting was convened in February 2019. Sadly, one of the PPI members passed away. His wife felt very strongly that she would like to take his place on the TSC, and this was agreed. Like the IDSMC, the TSC would expect to meet at least annually. In D-CODE there was a total of three TSC meetings.

4.7 Intervention

4.7.1 Vitamin D Preparation

Vitamin D supplementation is often given in conjunction with calcium supplementation or as a combined therapy where musculoskeletal effects are desired. However, calcium supplementation may cause gastro-intestinal side-effects (Grant et al., 2005b). A randomised, placebo-controlled trial of fracture prevention in elderly people, found that participant compliance was better with vitamin D supplementation alone rather than combined with calcium. Compliance with vitamin D therapy was over 80% in this trial (Grant et al., 2005b). The purpose of D-CODE was to explore non-skeletal benefits therefore a vitamin D only supplement was used to minimise side effects and aid compliance.

While there is no agreement regarding required dose of vitamin D supplementation for patients with CD, studies have suggested that higher doses are more effective. In a small study of 21 patients with CD, Hiew et al., (2013) found patients given a high dose vitamin D supplement (50,000IU weekly, equates to approximately 7100IU daily) (n=15), increased vitamin D levels by 150% compared to only a 29% increase in those receiving a lower dose vitamin D supplement (800IU daily) (n = 5). In a randomised controlled pilot study, Narula et al., (2017) compared vitamin D levels in CD patients randomised to receive either 1,000IU D3 daily (n=18) or 10,000IU D3 daily (n =16) for 12 months. Mean baseline serum level of participants was 72nmol/l, therefore, participants were not vitamin D deficient but the high dose vitamin D3 supplement was more effective at raising serum vitamin D levels. No adverse events were noted with the higher dose. A recent meta-analysis of 18 RCTs involving 908 patients showed higher doses to be more effective than lower doses of vitamin D,

and lower doses more effective than control (Li et al., 2018) at raising serum levels of vitamin D.

4.7.1.1 Rationale for Vitamin D and Dose

Within D-CODE participants were randomised via web-randomisation to either Arm A or B to receive different doses of vitamin D. Vitamin D3 is recommended by the National Osteoporosis Society (Francis et al., 2018) as being the most effective form of vitamin D supplementation compared to vitamin D2 (section 1.2.6). All doses of vitamin D either had UK Marketing Authorisation or were otherwise commercially available in the UK and available via normal NHS procurement. As there was no placebo and all participants received a vitamin D supplement, study participants were not blinded and were made aware after randomisation which dose they would receive. This pragmatic decision reduced costs in terms of pharmacy management of the supplements.

4.7.1.1.1 *Arm A Low dose regimen:* Vitamin D 400IU once daily for 24 weeks

Although some studies have suggested that a dose of 400IU is too low to be effective (Suibhne et al., 2012), particularly in patients with malabsorptive disorders, 400IU remains the standard dose recommended by NICE (2017) for treatment of 'at risk' groups

4.7.1.1.2 *Arm B High dose regimen:* Vitamin D 3,200IU once daily for 12 weeks;

followed by vitamin D 800IU once daily for a further 12 weeks.

The National Osteoporosis Society recommend a loading dose followed by a maintenance dose regimen in the treatment of vitamin D deficiency (Francis et al., 2018). The European Food Safety Authority (2012) set an upper tolerable limit of

4,000IU daily in adults. The dose recommended by the Endocrine Society to treat vitamin D deficiency in those over 8 years old is 4,000IU (Holick et al., 2011). It is feasible that a higher dose regimen of vitamin D, than that recommended by NICE, would offer greater clinical benefits in patients with CD in terms of effectively treating their vitamin D deficiency. A 3,200 IU capsule was chosen as the maximum licensed dose available commercially in a single capsule. This ensured that participants in both treatment arms were required to take only one capsule per day.

4.7.2 Treatment Period

The total treatment period was 24 weeks for both arms. This was a reasonable amount of time for vitamin D levels to increase with supplementation (Francis et al., 2018) and for any changes in patient reported outcomes to be recognised. In their meta-analysis, Li et al (2018) found that the effects of vitamin D supplementation were most pronounced in those with a treatment period of ≥6months (i.e., at least 24 weeks).

4.7.2.1 Known and Potential Risks

As per the SmPC the main known risk of taking vitamin D is the development of hypercalcaemia and hypercalciuria (uncommon >1/1,000 <1/100) and pruritus, rash and urticaria (rare >1/10,000 <1,000). Risks of treatment were minimised via study inclusion and exclusion criteria.

4.7.2.2 Assessment of Compliance with Study Treatment

Participants were given a daily treatment diary, which required them to tick each day that they had taken their vitamin D supplement or provide a comment if they had not. In addition, a verbal report by participants was recorded regarding their compliance,

as recommended by the PPI members in the TSC (Fletcher et al., 2021c). Participants reported if they had taken none, some, most or all their vitamin D capsules since their last study visit.

4.7.3 Amendment to supply of IMP due to Covid-19

To reduce face-to-face contact during the COVID-19 pandemic, verbal consent was gained from participants for posting of supplies of IMP by pharmacy, to their home address via a tracked delivery service where necessary. Participants were provided with a reply-paid envelope to return any unused IMP they had remaining at the end of the study.

4.8 Outcome Measures

In evaluating the effectiveness of research, healthcare interventions and treatment targets the measurement of outcomes is key. Over recent years there has been a move towards standardising which outcomes should be measured for specific disease states. The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD) proposed treatment targets which include clinical remission, endoscopic response, and improvement in biochemical measures as a guide for clinicians (Turner et al., 2021). A further proposal is the use of core outcome sets (COS), to ensure parity and consistency in both treatment and research. The Core Outcome Measures in Effectiveness Trials (COMET) initiative seeks to address this. In addition, the aim of the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) (Mokkink et al., 2014), is to improve the selection of outcome measurement tools used in research but also to encourage the development of COS.

A COS was devised for adults with IBD in clinical practice (Kim et al., 2017). Four key elements were considered in the development of the COS including i) survival and disease control (e.g., disease activity and anaemia) measured by a disease index, ii) health care utilisation (e.g., hospital admissions), iii) disutility of care (e.g., disease complications and steroid use), iv) symptoms, function and quality of life measured by patient reported outcome measures (PROMS). However, it was later recognised that these outcomes did not cover issues specific to patients with CD. Therefore, a similar COS was devised for patients with fistulating perianal CD (Sahnan et al., 2019). These recommendations again included clinician assessments, imaging and patient reported outcomes.

4.8.1 Patient Reported Outcome Measures

The US Food and Drug Administration (USFDA) (2009) define a PROM as any report of the status of a patient's health that comes directly from the patient. This is without interpretation of the patient's response by a clinician or anyone else and without laboratory assessments. There may be both generic health utility measures and disease specific measures. The benefit of a disease specific PROM is in collecting patients' perceptions of how their disease impacts on their quality of life specifically – rather than the overall effect of their general health, although both may be of interest. Bojic et al., (2016) described 23 different IBD related PROMS, including shortened forms, that have been developed to capture the patient's perception of their disease.

4.8.2 Selection of Disease Specific PROMS for D-CODE - Methodology

The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) guidelines (Turner et al., 2021) recommend the use of the PRO2 tool (Khanna et al.,

2015) as a PROM to measure the patient's perspective of clinical response in IBD. The PRO2 is based on elements of the Chron's Disease Activity Index (CDAI), taking two patient reported questions from this only (abdominal pain and stool frequency), because there is evidence that these contribute the majority of variance in the total CDAI score. The PRO2 was validated against the full disease index (Khanna et al., 2015) and the authors suggest that these two questions could be used alone to meet the requirements of the USFDA to include a PROM within research. However, this assumes that a full suite of other outcome measures is also included (Turner et al., 2021). The use of a complete disease index can provide patient reports of symptoms as well as more objective measures of disease severity and would usually be desirable in effectively evaluating research outcomes, with a validated PROM providing a different and additional element of evaluation.

Therefore, several disease specific PROMS were assessed prior to selection for D-CODE. In IBD there are PROMS capturing disease related quality of life and those related to disability caused by the disease. Allen et al., (2013) describe disability as relating to the restrictions and limitations on normal activity caused by the disease, where disease related quality of life is the subjective feelings and experiences of the patient. A PROM that captured wider disease related quality of life rather than disability was preferred, although both types of PROMs were reviewed.

4.8.2.1 Search Strategy

To focus on published and validated tools that met the criteria of a PROM the COSMIN database of systematic reviews on PROMS was searched. Using the search term 'IBD' captured all relevant articles related to UC, CD and IBD. There were seven systematic reviews related to IBD. One systematic review claimed

evaluation of PROMs, but the included tools were mostly disease indices and did not entirely meet the definition of a PROM. Four systematic reviews were discounted in total. Figure 4-2 shows the flowchart of the search strategy and results.

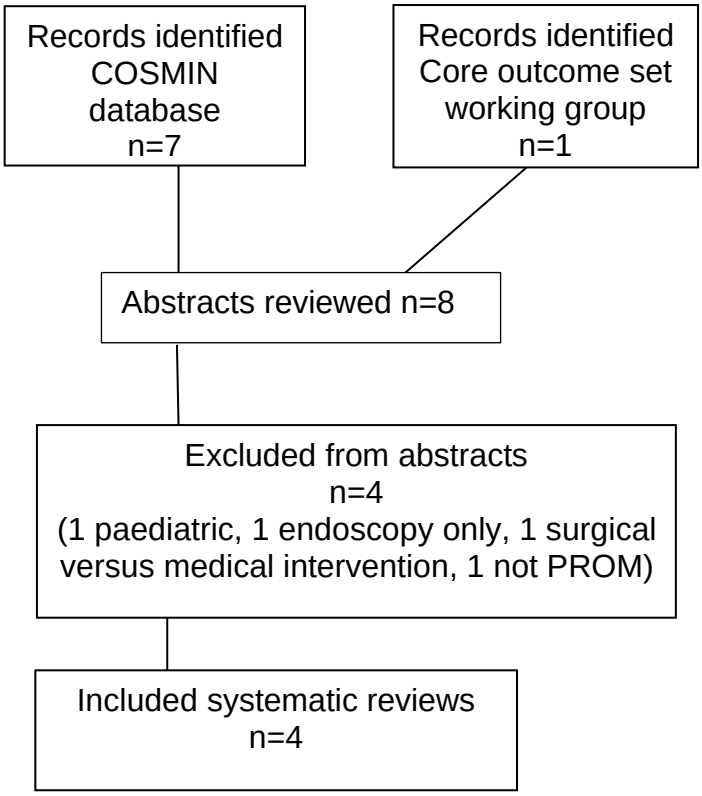


Figure 4-2: Search results for IBD PROMS identified from the COSMIN database

4.8.2.2 Evaluation of Disease Specific Patient Reported Outcome Measures

Aims were i) to gain an initial impression of the ease of administration and understanding the questions, ii) gain an understanding of the type of information likely to be elicited from patient responses and iii) to determine if this would detect a change in quality of life over a 6-month intervention period as per the study primary outcome.

The recall period of the PROM was important. Patients completed the PROM at the beginning and end of the 6-month intervention. A long recall period is likely to be less reliable due to memory but may have also meant that patients were recalling

symptoms/emotions from long before the intervention was complete. In terms of analysing and interpreting results after such a short intervention, a maximum two-week recall period seemed reasonable.

Twenty-one PROMS were identified and reviewed in four systematic reviews. Where PROM tools were accessible, the tool was reviewed directly. Where the tool was not available separately but an example of it was reproduced in the original article, the article version was reviewed. Where neither version of the tool was available, the description of the tool from the original article where full text was available was used. Where the original PROM full text was not available, the description given in the systematic review articles was used.

Of the 21 PROMS identified, ten were discounted due to a prolonged, speculative, undefined, or unclear recall period. A further three PROMS were either particularly clinically/surgery focused or did not fully evaluate quality of life but focused on patient concerns (not impact). Neither of the two disability-focused PROMS were suitable due to a long recall period or the administration method, where the interviewer read aloud questions and the patient responded. A self-administered method was preferred. Of the seven PROMS remaining to be assessed, five of these were different versions of the Inflammatory Bowel Disease Questionnaire (IBDQ)(Guyatt et al., 1989), and two were different versions of the Crohn's and Ulcerative Colitis Questionnaire (CUCQ)(Alrubaiy et al., 2015a).

All four of the systematic reviews critically appraised the included PROMS for validity, consistency, responsiveness, and reliability (Fletcher et al., 2021b). However, in developing the COS, Kim et al., (2017) were seeking specific domains and so

additionally assessed PROMS against their chosen domains and applicability to everyday clinical practice. They recognised that the IBDQ was used most often in research. However, they recommended the IBD-Control questionnaire (Bodger et al., 2014) as a quick and easy tool to use in clinical care that did not require a license for use. The other three reviews concluded that the IBDQ-32 was the most widely used and published instrument with good reliability and validity (Chen et al., 2017, Pallis and Mouzas, 2000, Alrubaiy et al., 2015a). Comparability of results between trials is an additional benefit of using of tool that has been used extensively in other studies (Fletcher et al., 2021b). Table 4-1 gives an overview of the 21 PROMs reviewed, including key elements such as method of administration and recall period.

Table 4-1: Overview of IBD PROMS

Outcome measure	Cited in systematic review	Disease	Method of administration	Recall period	Comment
32-item Inflammatory Bowel Disease Questionnaire (IBDQ-32) (Guyatt et al., 1989)	Chen et al. (2017) (Alrubaiy et al., 2015b) (Pallis and Mouzas, 2000) (Kim et al., 2017)	IBD	Self	2 weeks	Has a version for those with or without a stoma. Extensively validated.
Short Inflammatory Bowel Disease Questionnaire (SIBDQ) (Irvine et al., 1996)	(Chen et al., 2017) (Alrubaiy et al., 2015b) (Kim et al., 2017)	IBD	Self	2 weeks	Derived from IBDQ for community use in general practice. Query over suitability for clinical trial use.
36-item Inflammatory Bowel Disease Questionnaire (IBDQ-36) (Love et al., 1992)	(Chen et al., 2017)	IBD	Self	2 weeks	Unable to access directly. As per the IBDQ-32 but with an additional functional element. Less well validated in comparison to the IBDQ-32 (Chen et al., 2017).
9-item Inflammatory Bowel Disease Questionnaire (IBDQ-9) (Alcalá et al., 2004)	(Chen et al., 2017) (Alrubaiy et al., 2015b) (Kim et al., 2017)	IBD	Self	2 weeks	Shortened version of IBDQ-32, less extensive and so unlikely to fully establish change in quality of life related to the intervention.
The Rating Form of IBD Patient Concerns (RFIPC) (Drossman et al., 1991)	(Chen et al., 2017) (Alrubaiy et al., 2015b) (Pallis and Mouzas, 2000)	IBD	Self (25 questions)	Today	Aim is to elicit patient concerns rather than to determine actual disease impact on their quality of life.
The Cleveland Clinic Questionnaire for Inflammatory Bowel Disease (CCQIBD) (Farmer et al., 1992)	(Chen et al., 2017) (Pallis and Mouzas, 2000)	IBD	Self - interview (47 questions)	2 months	Unable to access. Limited evidence available for their validity noted by Chen et al (2017). Recall period too long.

Outcome measure	Cited in systematic review	Disease	Method of administration	Recall period	Comment
The Padova Inflammatory Bowel Disease Quality of Life (PIBDQL) (Martin et al., 1995)	(Chen et al., 2017) (Pallis and Mouzas, 2000)	IBD	Self (Chen et al 2017)	NA (Chen et al 2017)	Unable to access. Limited evidence available for their validity noted by Chen et al (2017)
The Cleveland Global Quality of Life (CGQL) (Fazio et al., 1999, Kiran et al., 2003)	(Chen et al., 2017)	IBD	Self (3 questions, scale 0-10)	Today	Unable to access. Based on patients having surgery (Chen et al 2017)
The Short Health Scale (SHS) (Hjortswang et al., 2006)	(Chen et al., 2017)	UC	Self (4 questions, visual analogue scale)	No set time scale	Not validated for CD.
The Edinburgh Inflammatory Bowel Disease Questionnaire (EIBDQ) (Smith et al., 2002)	(Chen et al., 2017) (Alrubaiy et al., 2015b)	IBD	Self (15 questions)	2 weeks	Clinical focus – first two questions ask if they have been given enough information about their disease and the contact details for a patient support group. Not all entirely relevant to research aims. Nothing specific regarding those with a stoma.
The Crohn's Life Impact Questionnaire (CLIQ) (Wilburn et al., 2015)	(Chen et al., 2017)	CD	Self (27 questions)	Unclear	Benefit of being specific to CD. Unable to evaluate fully as the final questionnaire is not available. Unclear recall period from the article.
The Crohn's and ulcerative colitis questionnaire (CUCQ-32) (Alrubaiy et al., 2015a)	(Chen et al., 2017) (Kim et al., 2017)	IBD	Self (32 questions)	2 weeks	Clear questions, easy to complete. Only relevant to those without a stoma (mentions bowels opened – not stoma bag emptied).

Outcome measure	Cited in systematic review	Disease	Method of administration	Recall period	Comment
The Crohn's and ulcerative colitis questionnaire (CUCQ-8) (Alrubaiy et al., 2015a)	(Kim et al., 2017)	IBD	Self (8 questions)	2 weeks	Shortened version of CUCQ-32, less extensive and so unlikely to fully establish change in quality of life related to the intervention.
The UK-IBDQ (Cheung et al., 2000)	(Kim et al., 2017)	IBD	Self (32 questions derived from the IBDQ)	2 weeks	From the article ascertained that it is almost the same as the IBDQ but more English terms used – not as extensively validated. No reason to use this instead of the IBDQ
The IBD disability score (Allen et al., 2013)	(Alrubaiy et al., 2015b)	IBD	Self (44 questions)	1 month	Questions focused on disability rather than patient experience of the disease. Recall period a little long for the study aims
The IBD disability index (Peyrin-Biroulet et al., 2012)	(Alrubaiy et al., 2015b)	IBD	Interviewer reads aloud to the patient (19 questions plus clinical parameters)	1 week	Disliked the element that the interviewer reads aloud a list of questions. Puts the patient under pressure to answer quickly, less time for them to fully understand the question than if they were reading it themselves. Focus on disability.
Social Impact of Chronic Conditions–Inflammatory Bowel Disease (SICC-IBD) questionnaire (Smith et al., 2012)	(Alrubaiy et al., 2015b)	IBD	Self (8 questions)	Ever	Specifically looking at social impact e.g. work, earnings, family relationship. Not entirely relevant to research aims. Also need to define recall period as intervention study.

Outcome measure	Cited in systematic review	Disease	Method of administration	Recall period	Comment
Crohn's Disease Perceived Work Disability Questionnaire (CPWDQ) (Vergara et al., 2011)	(Alrubaiy et al., 2015b)	CD	Self (16 questions)	1 year	Recall period is too long -intervention study over a much shorter period.
Crohn's disease burden questionnaire (Wilcox et al., 2010)	(Alrubaiy et al., 2015b)	CD	Self (4 questions, responses marked on a 'feeling thermometer')	2 weeks then speculative to the future	Speculative element is not useful or relevant to research aims
Ulcerative colitis and Crohn's disease Health Status Scales (Drossman et al., 1992)	(Pallis and Mouzas, 2000)	IBD	Unclear	Unclear	Unclear usage
The IBD-Control (Bodger et al., 2014)	(Kim et al., 2017)	IBD	13 questions plus a visual analogue scale	2 weeks then speculating about what they wish to discuss at the next clinical appointment	Clinically focused, questions not relevant to the research aims. Asks what would you like to discuss at your next appointment – not relevant to a research follow up.

Key evaluation parameters included a recall period that was no greater than two weeks and a preference for self-administration of PROMs given that these may be posted to participants. PPI identified that questions must relate to participants with or without a stoma. Questions needed to address the research aim, being a change in health-related quality of life. Those that were specifically clinically focused were less likely to be relevant, overall, to the research aims.

4.8.2.3 Patient and Public Involvement

The Expert by Experience-IBD group had been involved in selecting PROMs for the study. The group identified that some of the PROMS were lengthy, which they felt may affect completion rates. This is broadly supported in the literature. A systematic review including 481 RCTs, showed that shorter questionnaires increased questionnaire response rates (1.64; 95% CI 1.43 to 1.87; P < 0.00001, I(2) = 91%) (Edwards et al., 2009). A study of 1000 participants, who were randomly selected to receive one of four different questionnaire packs, also found shorter questionnaires improved response rate (OR = 1.48, 95% CI 1.06 to 2.07) (Sahlqvist et al., 2011). Conversely, a small study of 28 participants in a prostate cancer pilot study, found that longer questionnaire length increased the likelihood of participation in the study (Koitsalu et al., 2018), although this is a much smaller sample size than the previously described studies.

The PPI group identified that it was important for the language used in the PROM to be relatable to those with or without a stoma. Use of language referring to 'having bowels opened' was not applicable to people with a stoma, as this was unrelatable to their experience of emptying their stoma bag. This was an essential consideration in ensuring compliance with PROM completion. A variety of PROMS were reviewed by the PPI group. The IBDQ (Irvine, 1999) was suggested as the main disease specific PROM. The IBDQ has two versions available: one for those with a stoma and one for those without.

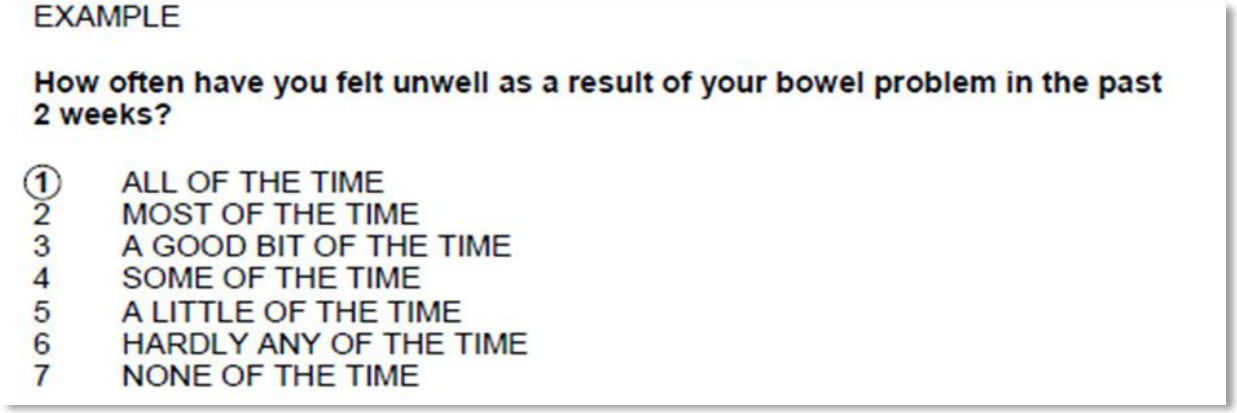
Therefore, considering requirements of the PROM to meet PPI recommendations, study aims and to ensure a reliable and valid tool was used, the IBDQ-32 was chosen

as the disease specific PROM for D-CODE. This decision was supported by the findings of the literature review (section 4.8.2.1).

4.8.2.4 The Inflammatory Bowel Disease Questionnaire

The IBDQ is copyrighted to McMaster University, USA and can only be used after purchase of a licence for use. For the purposes of D-CODE a student/academic licence for USD150.00 was purchased. However, for a full clinical trial the cost of the licence would be several thousands of dollars. It would be important to include this cost in any funding application.

The IBDQ includes 32 questions with graded responses 1 to 7. The questions explore IBD symptoms, general well-being, and mood over the preceding two weeks. Figure 4-3 gives an example of the question format. IBDQ score is calculated by adding scores for all 32 questions and ranges from 32 to 224, with a higher score indicating a better health related quality of life.


EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

(1) ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Figure 4-3 Example of question format in the IBDQ. Participants circled the response that was most relevant within the previous two-week period.

4.8.3 Selection of a Generic Health Utility Measure for D-CODE

A generic health utility measure looks at domains of general health rather than focusing on the effects of a specific disease. A generic health measure was included to try to capture elements of patient perception that may not be captured in the IBDQ. Several systematic reviews have suggested that the Rand Healthcare Short Form (36) (SF-36) and Euroqol EQ-5D are commonly used generic measures in a variety of conditions (Haywood et al., 2005, Geraerds et al., 2020, Izadi et al., 2018) with the EQ-5D validated in patients with IBD (Stark et al., 2010). The SF-36 contains 36 items including those related to physical health, restriction on activities due to physical health and emotional restrictions. Recall period varies between 'now' and in the last 4 weeks. The SF-36 is in the public domain and freely available without the need for a license.

The EQ-5D consists of 2 parts including 5 descriptive questions and the EQ visual analogue scale (EQ VAS). The descriptive questions cover five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ VAS records the patient's self-rated health on a vertical visual analogue scale, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine.' Recall period is today. Registration is required for use, but this is free of charge.

The PPI group agreed with the addition of EQ-5D-5L (Herdman et al., 2011) as a short generic health utility measure. The group agreed that EQ-5D-5L was an easy to use, concise measure with a short recall period (Stark et al., 2010). Inclusion of

the IBDQ-32 and EQ-5D-5L offered complete coverage of important symptoms, signs, and patient experience with the least possible duplication. Table 4-2 shows a comparison of the domains explored in each selected PROM.

Table 4-2 Comparison of Domains

IBDQ Domains	EQ-5D-5L Domains
Bowel systems	Mobility
Emotional health	Self-care
Systemic systems	Usual activities
Social function	Pain/discomfort
	Anxiety/depression
	Visual analogue scale – health status today

4.8.4 Patient Reported Outcome Measure Administration

Both the IBDQ (with and without a stoma versions) and EQ-5D-5L were presented by the data management team at the CTU as a single booklet in English only (Appendix 10). Although both PROMS are available in a variety of languages, English language booklets only were produced after discussing this issue with the Public Engagement office at UHBFT. The two key reasons were:

- Birmingham is an ethnically diverse city; therefore, it would be difficult to provide a booklet in every language that patients may have spoken
- It cannot be assumed that because patients speak a language that they can also read the same language. Illiteracy is high among some ethnic minority groups (Dein and Bhui, 2005)

Where patients could not read English, a hospital-based interpreter would be organised according to their needs.

PROMS were administered at the randomisation appointment and at 24-weeks (after 6 months of intervention). Initially, PROMS were administered during a face-to-face consultation in the first period of recruitment but then as a postal questionnaire following amendments made to processes due to the COVID-19 pandemic.

4.8.5 Closing participant experience questionnaire

A short closing questionnaire (Appendix 10) was posted to participants prior to their final, 28-week telephone follow up appointment, with a pre-paid return envelope for return. This was a simple a questionnaire to explore participants experience and views towards being involved in research, as per previous research carried out by the NIHR Clinical Research Network (Clinical Research Network Co-Ordinating Centre, 2019). The questions were rated on a 5-point scale with 1 being ‘strongly disagree’ and 5 being ‘strongly agree’.

Questions/statements were:

1. I would be happy to take part in another research study
2. I had a good experience of taking part in the research study
3. Free text - please tell us more about your answers

4.8.6 Diet and Lifestyle Questions

At the final 28-week appointment, data collection from the original vitamin D screening study on diet and lifestyle (sections 3.5.4 and 3.5.5) was repeated. The purpose of this was to establish if participants had changed their diet or lifestyle since participating in the vitamin D supplementation trial and if they had continued to take vitamin D supplements beyond the intervention period.

4.8.7 Disease Indices

A disease index is a list of clinical parameters that indicate the activity of a disease. A score is assigned to each parameter to give an overall score that is indicative of disease activity. Although parameters may include patient description of symptoms, such as frequency of bowel movements and pain, unlike a PROM they may also contain physician assessments and/or biochemical measures. Several disease indices have been developed for IBD in the absence of a gold standard marker of disease activity or remission (Bojic et al., 2016). Although the standard set of outcome measures for IBD recommends the Manitoba IBD Index (Clara et al., 2009) as a simple tool to use in clinical practice, it is a generic IBD measure and not specific to CD.

The Crohn's Disease Activity Index (CDAI) (Best et al., 1976) is commonly used in research to assess clinical remission in CD. A CDAI score of less than 150 is considered clinical remission - score range is 0 to 600 with higher scores indicating more severe disease. The Harvey-Bradshaw Index (HBI) (Harvey and Bradshaw, 1980) is an alternative tool that is a simplified version of the CDAI (Best, 2006). Score 3 or less indicates remission. Patients with a score of 8 to 9 or higher are considered to have severe disease. Although it is acknowledged that the CDAI is a complex tool to use, it remains the preferred disease index in CD clinical trials (Best, 2006).

A recent systematic review by Catt et al (2019) included 181 clinical trials in CD. They found that the CDAI was used to define remission or disease response, appearing in 77.9% of trials, with the HBI used in only 6.6% of trials.

Given the breadth of information collated in the CDAI compared to the HBI it provides a thorough assessment of disease activity. The CDAI has been criticised for poor correlation with objective signs of inflammation detected by endoscopy (Regueiro et al., 2010), and it is recommended that inflammatory biomarkers as well as symptom reports are used to guide clinical decisions. Therefore, the CDAI was appropriate as part of the battery of assessments in D-CODE to provide indication of likely disease activity at baseline, 12 and 24 weeks.

Completion of the CDAI required collection of information from the patients, and from the patients' records for haematological measures and clinical features, such as abdominal masses (Table 4-3). Collated information was input to the online CDAI calculator recommended by the European Crohn's and Colitis Organisation www.ibdsupport.org.au/tools/cdai-calculator/. This calculator generated the score.

Table 4-3 Crohn's Disease Activity Index elements

Information required	Information source	Score weighting factor
Number of liquid or soft stools each day (last 7 days)	Patient report	x 2
Abdominal pain (graded from 0-3 on severity) each day (last 7 days)	Patient report	x 5
General well-being, subjectively assessed from 0 (well) to 4 (terrible) each day (last 7 days)	Patient report	x 7
Current presence of complications (e.g., anal fissure, arthralgia)	Patient report and clinical letters	x 20
Current use of anti-diarrhoeal agent	Patient report and clinical letters	x 30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	Clinical letters	x 10
Haematocrit of <0.47 in men and <0.42 in women	Clinic blood samples	x 6
Current height and weight (calculation of percentage deviation from standard weight)	Patient weight in clinic	100 x (1 − (current/ standard))

4.8.8 Secondary Aim Outcome Measure

The secondary aim, to investigate the role of the researcher in a hybrid study with the researcher carrying out trial co-ordination, was measured by reflective practice (4.17.7 and Appendix 11).

4.9 Biochemical measures – safety, efficacy, novel

Biochemical measures were taken at baseline, 12 weeks and 24 weeks for safety, efficacy, and novel research investigation. Samples were taken via venepuncture by trained phlebotomists in the out-patient clinic and trained nurses in the infusion unit. Samples for safety and efficacy were analysed at UHBFT clinical biochemistry laboratories.

4.9.1 Sample collection COVID-19 amendments

Following the first wave of the UK COVID-19 pandemic, few patients were attending hospital except for essential treatment. COVID-19 management strategies were employed in an amended D-CODE Protocol V5.0 13/10/2020 (Appendix 6) to enable continued recruitment and to maintain participant safety. The amendment included, where participants were not able to attend the hospital for blood tests or delivery of faecal calprotectin samples, these were arranged at an off-site phlebotomy centre. Hepcidin and vitamin D metabolites were not collected at an off-site centre due to challenges with tracking research samples.

Where participants were self-isolating and were not able to attend for blood tests within the follow up window, vitamin D supplements were provided following assessment by the Principal Investigator (PI) and blood tests arranged at the earliest opportunity when the participant was no longer isolated. The aim was to organise

collection of samples and measurements of weight to coincide with other clinical hospital visits. Where participants were self-isolating and were not able to attend for blood tests or delivery of samples, these could be carried out at the participant's home address with their verbal consent and according to the Trust lone-worker procedure.

4.9.2 Safety

4.9.2.1 Vitamin D

Though, participants were identified from the vitamin D screening study with levels <50nmol/L, 25(OH)D was measured again at randomisation to ensure participants were still eligible to take part. There has been debate regarding the accuracy of some methods of analysing vitamin D samples, with liquid chromatography-tandem mass spectrometry and immunoassay being the two key methods, sometimes yielding different results (D. Carter, 2011, Bikle, 2018). In a study of 5915 blood samples, liquid chromatography-tandem mass spectrometry gave much higher results than immunoassay, with a mean difference of 25(OH)D 32nmol/L (Berry et al., 2017). However, the authors note that harmonisation of methods will reduce this. There may also be inconsistency within the same test method, particularly in immunoassay, although international standards and harmonisation are aiming to reduce this (Boucher, 2020). With the initial DBS analysed at a different laboratory using different methods, it was also important to establish the baseline level for blood samples processed at QEHB. QEHB laboratories routinely use the Abbott 2nd generation 25(OH)Vitamin D immunoassay™, which is a chemiluminescent assay (Hutchinson et al., 2017, Avci et al., 2020) opposed to the liquid chromatography-tandem mass spectrometry method described in section 3.5.1. Vitamin D was then measured again

at 12 and 24 weeks to monitor for vitamin D toxicity indicated by levels 25(OH)D >250nmol/l.

4.9.2.2 Corrected Calcium (calcium and albumin)

Given the recognised risk of hypercalcaemia associated with vitamin D supplementation, corrected calcium levels were measured at baseline to confirm eligibility. Corrected calcium was then measured again at 12 and 24 weeks to monitor for the development of hypercalcaemia.

Calcium appears in serum complexed with small anions (10%), bound to albumin (40%), and as free ionised calcium (50%) (O'kane et al., 2015). Although free ionised calcium represents the greatest quantity in serum there is currently no clinically available analysis for this form. Therefore, in clinical practice albumin-bound calcium is measured. This test is then subject to variation in reliability according to the patient's albumin status. To provide a more reliable result, albumin is measured to allow calculation of corrected, or adjusted, calcium serum levels (O'kane et al., 2015). Although the validity of this calculation has been questioned (Grzych et al., 2019, Smith et al., 2018, Lian and Åsberg, 2018); this continues to be standard clinical practice in the UK. Therefore, in D-CODE both calcium and albumin were measured.

4.9.2.3 Parathyroid Hormone (PTH)

PTH is a hormone secreted by the parathyroid gland that regulates serum calcium levels. Hypocalcaemia results in release of PTH that causes a mobilisation of calcium stores in the bone to increase serum calcium levels. Hyperparathyroidism is a condition where the parathyroid gland is overactive, releases too much PTH resulting in hypercalcaemia. Consequently, patients with known hyperparathyroidism were

excluded from the study. PTH was measured in the study to monitor for development of hyperparathyroidism during the study.

4.9.3 Efficacy

4.9.3.1 Iron Studies and Full Blood Count (FBC)

Iron studies and FBC were measured to determine the presence of iron deficiency anaemia and any changes in anaemia in response to vitamin D supplementation. Haematocrit results from the FBC was also required in the CDAI calculation.

4.9.3.2 C-Reactive Protein (CRP)

CRP is an acute phase protein produced by the liver and released in response to inflammation. In the study CRP was measured as an indication of CD inflammation and inflammatory changes in response to vitamin D supplementation. Although, CRP is a commonly used biomarker of inflammation in clinical practice, it is recognised that CRP is not the most reliable indicator of intestinal inflammation (Kyle et al., 2020). Hence, faecal calprotectin was also measured to provide an additional, more reliable indicator (section 4.9.4.3).

4.9.4 Novel biological compound measures

For the purposes of the D-CODE feasibility study, blood samples were collected for measurement of hepcidin and vitamin D metabolites as an exploratory exercise only. These may be areas for future research in patients with CD.

4.9.4.1 Hepcidin

Hepcidin is a peptide produced by the liver and the main regulator of iron homeostasis (Ganz, 2011). Hepcidin has been shown to be a mediator of iron deficiency anaemia in people with CD (Basseri et al., 2013). Studies have suggested

an association between vitamin D status, hepcidin and anaemia (Syed et al., 2017), with vitamin D suppressing the over production of hepcidin (Bacchetta et al., 2014). Thus, the relationship between hepcidin and vitamin D in this study is of interest in the development of iron deficiency anaemia. The QEHB laboratory process for managing these samples was as follows:

- Special instructions: centrifuge within 1 day. Store at -80°C until analysis.
- Samples will be transported in cold storage packaging to MIDRU Laboratory, Birmingham Heartlands Hospital for batch analysis when all samples are collected.

4.9.4.2 Vitamin D Metabolites

Although the primary objective of vitamin D supplementation trials is to raise circulating levels of 25(OH)D via activity of the enzyme 25-hydroxylase, it is clear from our fundamental knowledge of vitamin D physiology that other metabolic pathways may be impacted by the administration of oral vitamin D supplements. Conversely, the activity of other enzymes may modify the efficacy of 25-hydroxylase in response to vitamin D supplementation. In recent years, analytical chemistry studies have established new methodologies to measure multiple vitamin D metabolites in serum samples beyond the routine analysis of serum 25(OH)D (Jenkinson et al., 2016). The most prominent metabolites to be studied using this approach are: 1) $1,25(OH)_2D3$ – the active, hormonal form of vitamin D formed by 1α-hydroxylase metabolism of 25(OH)D3; 2) 3epi-25(OH)D3 – an epimerase variant of 25(OH)D3; 3) 24,25-dihydroxyvitamin D3 ($24,25(OH)_2D3$) – a 24-hydroxylated form of 25(OH)D3, representing catabolic, inactivation of vitamin D; 4) 25(OH)D2 – the D2 form of 25(OH)D which is found in some foods. In preliminary studies of

vitamin D in pregnancy (Tamblyn et al., 2017), and musculoskeletal ageing (Hassan-Smith et al., 2017), carried out at the University of Birmingham, analysis of multiple vitamin D metabolites, often termed the 'vitamin D metabolome' was shown to provide a greater range of clinical information compared to simple measurement of serum 25(OH)D. This was further confirmed using mathematical modelling studies which examined the information provided by multiple vitamin D metabolites relative to 25(OH)D alone (Beentjes et al., 2019). Based on these initial observations, it was decided to include multi-metabolite analysis of vitamin D as part of the feasibility study.

The QEHB laboratory process for managing these samples was as follows:

- Special instructions: centrifuge within 1 day. Store at -80°C until analysis.
- Samples will be transported to Steroid Metabolomics Analysis Core (SMAC), Institute of Metabolism and Systems Research University of Birmingham for batch analysis when all samples are collected. Samples will be collected on dry ice and an IMSR sample Receipt and Storage form will be completed. Prior to analysis samples will be stored in a GCP (Tutela Systems UKAS accredited) temperature monitored -80 freezer at the IMSR.

4.9.4.3 Faecal calprotectin

Calprotectin is a protein derived from neutrophils (Ayling and Kok, 2018) that is released during the inflammatory response. Calprotectin is found in a variety of body fluids but prominently in faeces where its concentration is approximately six times that found in blood (Ayling and Kok, 2018). The measurement of faecal calprotectin is recognised as a useful tool in diagnosing IBD and differentiating symptoms

between patients with functional/non-inflammatory diseases such as irritable bowel syndrome (An et al., 2019). In a recent systematic review and meta-analysis, An et al., (2019) found that in symptomatic patients with faecal calprotectin levels <50µ/g IBD could be reliably excluded. As such the measurement of faecal calprotectin has become a useful surrogate marker of intestinal inflammation in IBD (Burri and Beglinger, 2011, Herranz Bachiller et al., 2016, Stevens et al., 2019, D'haens et al., 2012). Studies have suggested the following interpretation of faecal calprotectin measurements in patients with diagnosed IBD:

- Levels <50 µ/g to 100 µ/g, quiescent disease is likely
- Levels >100 µ/g to 250 µ/g, inflammation is possible
- Levels >250 µ/g, active inflammation is likely

(Bressler et al., 2015, Turvill et al., 2017)

Given the recognised anti-inflammatory effects of vitamin D, within D-CODE stool samples for faecal calprotectin were collected at randomisation and at the end of treatment to determine changes in intestinal inflammation in response to vitamin D supplementation. Samples were analysed at UHBFT clinical biochemistry laboratories.

4.10 Study Size

As a feasibility study no formal sample size calculation was carried out by the CTU statistician. Instead, an estimate of total 50 participants (n=Arm A 25 + Arm B 25) across three sites was assumed to be sufficient to provide an indication of feasibility. Although, various sample sizes ranging from 24 to 50 have been suggested for

feasibility studies (Lancaster et al., 2004, Julious, 2005, Sim and Lewis, 2012) the supervisory team felt that a sample size in the upper range would allow the aims of the study to be addressed with more confidence, particularly as the study plan included three sites initially.

Target sample size for each hospital site was:

- QEHB – 20 participants
- BHH – 20 participants
- GHH – 10 participants

4.11 Statistical Methods

The CTU was commissioned by the Sponsor to carry out data management and statistical analysis for the trial. As per the CTU statistical analysis plan and D-CODE protocol, no comparative analyses were carried out. The main outcome measures are presented using summary statistics including frequencies, percentages, mean, median and interquartile range (Fletcher et al., 2021a). Analyses for the feasibility study were pre-specified in a CTU statistical analysis plan and were performed using SAS Institute Inc 2019, version 9.4, or later, where carried out by CTU statisticians. As described in section 3.8, to ensure data integrity and accurate analysis, JF was unable to participate in any analysis of data with this role reserved for the CTU statisticians. The number of patients screened for inclusion in the study, and the numbers eligible but not approached for consent, ineligible, not consented, and consented and recruited were summarised. The main outcome measures were presented using descriptive summary statistics as described in section 3.8. All randomised patients were included in the intention to treat analysis.

However, the COVID-19 pandemic prevented collection of data from some participants during April – July 2020. Thus, interpretation of CTU presented results is problematic as the impact of uncollected (rather than missing) data is not fully explained. Therefore, additional narrative is included to describe the results and feasibility outcomes adequately and more accurately. Although not part of the CTU statistical analysis plan or formal study results, a detailed examination of vitamin D metabolite results and the relationship between the metabolites is included for the purposes of discussion in this thesis.

4.12 Results

4.12.1 Participants

Previously described logistical issues at BHH and GHH prevented recruitment taking place at these sites. Therefore, results are presented for QEHB only. The incidence of COVID-19 remained high from 2020. Therefore, all strategies within the COVID-19 amendment, except the collection of samples from the patient's home, were employed to protect participants.

Figure 4-4 shows the CONSORT flow diagram for participant recruitment and Table 4-4 shows the overall study consent rate to be 47.1%.

Table 4-4 Overall Consent Rate

	n	%
Total patients screened	150	
Ineligible	90	60
Not approached for consent	9	6
Consent not obtained	27	18
Recruited	22	14.7
Consent rate		**47.1**

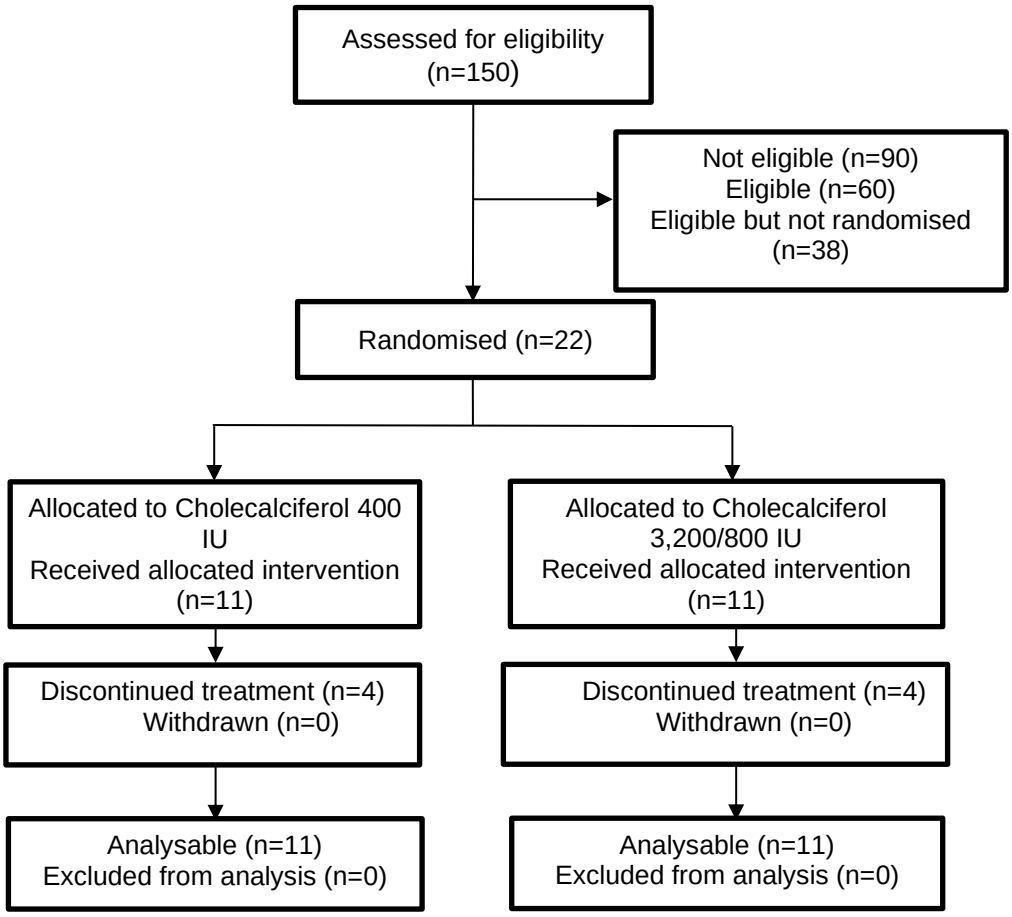


Figure 4-4 CONSORT flow diagram

The number of patients approached and consented did not vary when a comparison is made of the time before the COVID-19 pandemic and during the COVID-19 pandemic (Table 4-5). In total 24 patients were consented and 22 of these randomised. The recruitment period prior to the pandemic was three months and after the pandemic was 2 months.

Table 4-5: Comparison of Consent Before and During the COVID-19 Pandemic

Timepoint	Number of patients approached	Number of patients consented	Consent rate (%)
Prior to COVID-19 pandemic	25	12	48.0
During COVID-19 pandemic	26	12	46.2
Total	51	24	47.1

Overall, the two treatment arms were evenly matched in sex at birth, age, and ethnic diversity. Weight and height were broadly similar in both treatment arms (Table 4-6). Weight and height data were collected primarily for the calculation of the CDAI. Although these measurements are used to calculate body mass index (BMI), because BMI specifically was not included as a measurement in the original data and statistical analysis plan this could not be added once the study had commenced. Hence, BMI is not shown.

Table 4-6 Baseline Characteristics

Characteristic	Treatment Arm	
	A Cholecalciferol 400 IU	B Cholecalciferol 3,200/800 IU
Patients recruited, n	11	11
Sex at birth, n (%)		
Male	6 (54.5)	6 (54.5)
Female	5 (45.5)	5 (45.5)
Age (years)		
Mean (SD)	37 (15.1)	38.2 (17.5)
Median (IQR)	33 (23-53)	30 (24-56)
Range	18-59	19-69
Ethnicity, n (%)		
White British	8 (72.7)	8 (72.7)
Irish/British	0 (0.0)	1 (9.1)
Any other White background	1 (9.1)	1 (9.1)
White and Black Caribbean	1 (9.1)	0 (0.0)
Bangladeshi	0 (0.0)	1 (9.1)
African	1 (9.1)	0 (0.0)
Height (cm) at baseline		
Mean (SD)	172.5 (10.6)	172.5 (10.6)
Median (IQR)	172 (164-178.4)	177 (166-179.5)
Range	153.6-193	151.5-185
Weight (kg)		
Mean (SD)	71.6 (17.6)	77.8 (11.9)
Median (IQR)	67.5 (60.6-75.3)	74 (66.3-92.5)
Range	53.9-119.7	64.7-94.5

Table 4-7 shows the reasons for non-recruitment of patients and non-consent of eligible patients. Overall, 60% of those screened were not eligible on initial screening. Notable issues impacting recruitment include the Sponsor temporary halt preventing nine patients being approached, and time awaiting approval of a protocol amendment preventing two patients being consented at the time. In addition, several patients were found to be ineligible after initial screening which prevented recruitment rather than non-consent. However, this is not reflected in the reported consent rate.

Table 4-7 Reasons for Non-recruitment

Reason	n (%)
Not eligible at initial screening	**90 (60)**
Not identified as having vitamin D deficiency < 50 nmol l/ 25(OH)D	71 (78.9)
Currently receiving prescribed vitamin D containing supplementation	12 (13.3)
Currently receiving Bisphosphonates	1 (1.1)
With known renal disease or kidney stones	2 (2.2)
With known underlying liver disease	1 (1.1)
Who are pregnant, breast feeding, trying to conceive or woman of child-bearing capacity who decline to have pregnancy test and/or decline to take effective contraceptive measures during the intervention period	3 (3.3)
Eligible patient not approached	**9 (6)**
Sponsor halt	9 (100)
Eligible at initial screening but consent not obtained	**27 (18)**
Patient did not respond after being approached	4 (14.8)
**GP now prescribed vitamin D supplement*	*3 (11.1)*
**No longer vitamin D deficient on subsequent serum sample*	*3 (11.1)*
Does not want to take part in research	3 (11.1)
Does not want to take vitamin D supplement	2 (7.4)
***Awaiting protocol amendment to be approved for generic vitamin D*	*2 (7.4)*
Does not want to stop OTC vitamins	2 (7.4)
Unwilling to provide a reason	2 (7.4)
Does not want to be randomised	1 (3.7)
Concerned about allergies	1 (3.7)
Does not have time for study visits	1 (3.7)
Personal reasons	1 (3.7)
Vegan	1 (3.7)
Rebooking appointment	1 (3.7)
Consented but not randomised	**2 (1.3)**
Doctor concerned regarding deteriorating renal function	1 (50)
No longer vitamin D deficient >50mmol/L	1 (50)

*Participants were ineligible after initial screening rather than consent not obtained. ** A delay in gaining a protocol amendment prevented recruitment rather than consent not obtained.

4.13 Participant retention

4.13.1 Study withdrawals

No participants withdrew from the study.

4.13.1.1 Impact of the COVID-19 Pandemic on Follow up

As of 1st April 2020, 11 patients were randomised and active in the D-CODE vitamin D supplementation trial at varying stages of the study pathway. Of these, six participants had completed their 12 week follow up and received their final supply of vitamin D and five participants were due for their 12 week follow up within the forthcoming month. Due to the suspension of research, further research activity was suspended, although recruited participants remained in the study. A sponsor approved letter was sent to participants explaining the situation and advising them how to contact JF during the lockdown if they experienced any adverse effects from their vitamin D supplements, as adverse event data was still being collected.

During July 2020, UHBFT carried out an assessment of all research that had been in progress at the Trust prior to the pandemic. Following a structured review of the study viability in the light of COVID-19, UHBFT as Sponsor confirmed that D-CODE activity could recommence at QEHB if measures could be taken to protect participants during the COVID-19 pandemic.

However, by this time seven participants were already past the point of their final 28-week follow up and it was not possible to collect any further data from them. This resulted in missing data from these participants. The remaining four participants were just within the window for their final 28-week follow up appointment as per the

approved protocol at the time (V4.0 04/03/2020) and therefore 28-week data was collected as per the final appointment for these participants.

4.14 Completion of Trial Processes

4.14.1 Participant Follow up Attendance

All participants who were invited to follow up appointments attended either in person or via telephone appointment as per the protocol. All study procedures were carried out at the follow up appointments as per the protocol, except those shown in protocol deviations (section 4.14.7). Just one IBDQ/EQ5D5L and one participant experience PROM were not returned and one blood test for hepcidin/vitamin D metabolites not collected (all safety bloods were collected).

As per section 4.5.1.1, the total number of participants eligible and invited to attend each follow up appointment was:

- Eligibility n = 22
- 12 week follow up n = 17
- 24 week follow up n = 11
- 28 week follow up n = 15

4.14.2 PROMS

4.14.2.1 IBDQ & EQ5D5L

The IBDQ score ranges from 32 to 224 with a higher score indicating a better quality of life. Scores in all domains (Table 4-8) except for systemic systems show a downward trend in Arm A. In Arm B there is an improvement in emotional health and systemic systems but a downward trend in bowel systems and social function. Overall scores in both groups have reduced slightly.

Table 4-8 IBDQ 32 Results

		Arm A Cholecalciferol 400 IU		Arm B Cholecalciferol 3,200/800 IU	
		Eligibility	Week 24	Eligibility	Week 24
Domain	Total n	11	6	11	4
Bowel systems	Total (n)	9*	6	11	4
	Mean (SD)	52.1 (15.3)	52.0 (10.4)	55.6 (8.1)	51.3 (15.2)
	Median	60.0	50.5	59.0	51.0
	IQR	44.0-65.0	43.0-64.0	50.0-62.0	41.0-61.5
	Range	29.0-67.0	40.0-64.0	41.0-67.0	33.0-70.0
	Missing/Not valid	2	5	0	7
Emotional health	Total (n)	10*	6	11	4
	Mean (SD)	56.8 (18.4)	54.5 (14.3)	58.4 (15.4)	63.0 (19.6)
	Median	62.0	49.5	61.0	66.5
	IQR	34.0-73.0	43.0-67.0	48.0-69.0	47.0-79.0
	Range	28.0-78.0	41.0-77.0	32.0-83.0	39.0-80.0
	Missing/Not valid	1	5	0	7
Systemic systems	Total (n)	11	6	11	4
	Mean (SD)	21.2 (7.2)	24.5 (5.6)	19.6 (7.4)	22.3 (8.5)
	Median	23.0	24.5	18.0	22.0
	IQR	15.0-29.0	19.0-30.0	13.0-25.0	15.0-29.5
	Range	11.0-29.0	18.0-31.0	8.0-34.0	14.0-31.0
	Missing/Not valid	0	5	0	7
Social function	Total (n)	10*	6	11	4
	Mean (SD)	28.5 (9.4)	27.2 (7.1)	32.1 (5.8)	27.3 (9.3)
	Median	33.5	26.5	34.0	29.5
	IQR	23.0-35.0	20.0-35.0	32.0-35.0	20.0-34.5
	Range	6.0-35.0	20.0-35.0	15.0-35.0	15.0-35.0
	Missing/Not valid	1	5	0	7
Total IBDQ score	Total (n)	10*	6	11	4
	Mean (SD)	159.4 (46.4)	158.2 (33.9)	165.4 (32.4)	163.8 (47.7)
	Median	178.3	155.0	171.0	161.5
	IQR	114.6-188.0	128.0-179.0	148.6-186.0	123.0-204.5
	Range	74.0-209.00	126.0-206.0	106.0-219.0	119.0-213.0
	Missing/ Not valid	1	5	0	7

*Indicates where some domains either had an invalid answer or were not answered and so were not included in the analyses.

EQ5D5L scores are shown in Table 4-9 with the visual analogue scale (VAS) shown in Table 4-10. The VAS is scored 0-100 with a higher score indicating a better health state.

Table 4-9 EQ5D5L Domain Results

		Arm A Cholecalciferol 400 IU		Arm B Cholecalciferol 3,200/800 IU	
		Eligibility n (%)	Week 24 n (%)	Eligibility n (%)	Week 24 n (%)
Total (n)		11	6	11	4
Missing		0	5 (45.5)	0	7 (63.6)
Domain	Problem Level				
Mobility	None	9 (81.8)	4 (36.4)	9 (81.8)	2 (18.2)
	Slight	0	0	2 (18.2)	2 (18.2)
	Moderate	1 (9.1)	2 (18.2)	0	0
	Severe	1 (9.1)	0	0	0
Self-care	None	10 (90.9)	5 (45.5)	9 (81.8)	4 (36.4)
	Slight	1 (9.1)	1 (9.1)	2 (18.2)	0
Usual activities	None	6 (54.5)	3 (27.3)	6 (54.5)	2 (18.2)
	Slight	3 (27.3)	1 (9.1)	4 (36.4)	2 (18.2)
	Moderate	1 (9.1)	1 (9.1)	1 (9.1)	0
	Severe	1 (9.1)	1 (9.1)	0	0
Pain/discomfort	None	4 (36.4)	2 (18.2)	4 (36.4)	1 (9.1)
	Slight	5 (45.5)	1 (9.1)	4 (36.4)	2 (18.2)
	Moderate	0	2 (18.2)	3 (27.3)	1 (9.1)
	Severe	0	1 (9.1)	0	0
	Extreme	2 (18.2)	0	0	0
Anxiety/depression	None	3 (27.3)	2 (18.2)	6 (54.5)	2 (18.2)
	Slight	5 (45.5)	1 (9.1)	4 (36.4)	2 (18.2)
	Moderate	2 (18.2)	2 (18.2)	1 (9.1)	0
	Extreme	1 (9.1)	1 (9.1)	0	0

Table 4-10 EQ5D5L Visual Analogue Score

	Arm A Cholecalciferol 400 IU		Arm B Cholecalciferol 3,200/800 IU	
	Eligibility	Week 24	Eligibility	Week 24
Total (n)	11	6	11	4
Mean (SD)	72.7 (21.6)	71.7 (17.5)	72.8 (18.6)	76.3 (21.8)
Median	80.0	70.0	75.0	77.5
IQR	60.0-90.0	60.0-80.0	65.0-90.0	57.5-95.0
Range	35.0-100.0	50.0-100.0	36.0-100.0	55.0-95.0
Missing (n)	0	5	0	7

Score was 0-100 with a higher score indicating better health

Despite the missing values shown in each table above, of all the IBDQ/EQ5D5L booklets given to participants, all were done and returned except one. This suggests that these PROMs were largely acceptable to participants who received them.

4.14.2.2 Participant Experience PROM

In total, 14 out of 15 participant experience PROMs were returned at the final 28 week follow up. The summary of responses is shown in Table 4-11. Across both treatment arms the majority of participants responded that they agreed/strongly agreed that they would be happy to take part in research again and that they had a good experience of taking part in research.

Table 4-11 Patient Experience Questionnaire Summary

Responses*	Arm A Cholecalciferol 400 IU group		Arm B Cholecalciferol 3,200/800 IU group	
	Number of each response to *'I would be happy to take part in another research study'*,	Number of each response to *'I had a good experience of taking part in the research study'*	Number of each response to *'I would be happy to take part in another research study'*	Number of each response to *'I had a good experience of taking part in the research study'*
	n (%)	n (%)	n (%)	n (%)
1	0	0	0	0
2	0	0	0	0
3	1 (9.1 %)	0 (0.0%)	1 (9.1 %)	1 (9.1 %)
4	1 (9.1 %)	2 (18.2 %)	1 (9.1 %)	1 (9.1 %)
5	6 (54.5 %)	6 (54.5 %)	4 (36.4 %)	4 (36.4 %)
Missing	3 (27.3 %)	3 (27.3 %)	5 (45.5 %)	5 (45.5 %)

*1 strongly disagree – 5 strongly agree

Table 4-12 displays the full list of participant responses with free text comments provided by participants. Common themes in comments include that it was made

easy for them to take part and that, generally, they would be happy to participate again.

Table 4-12 Patient Experience Questionnaire Individual Responses with Free Text Comments

	Allocation	Responses to 'I would be happy to take part in another research study'*	Comments	Response to 'I had a good experience of taking part in the research study'*	Comments
1	Treatment A - Low dose 400 IU	5	If research is beneficial to others, then I would be happy to take part.	5	Research explained well informative and interesting
2	Treatment B - High dose 3200/800 IU	5	I will always be happy to take part in any study.	5	
3	Treatment A - Low dose 400 IU	5	Happy to help and support	5	All staff professional and everything was easy and well explained
4	Treatment A - Low dose 400 IU	5	The RN made it really easy to keep on top of everything	5	wasn't stressful at all and was good to get my blood levels corrected whilst doing the study!
5	Treatment A - Low dose 400 IU	5	I'm happy to help with any research	5	The RN was very informative and all appointments was made with my hospital appointments.
6	Treatment B - High dose 3200/800 IU	3	Depends on type / what is involved	4	Good communication with what is involved Supplied everything needed
7	Treatment A - Low dose 400 IU	5		5	

8	Treatment B - High dose 3200/800 IU	5	It was simple, easy, the researchers were nice + I got free vitamins. Always happy to help especially if the research helps people.	5	Everyone was nice + didn't take up lots of my time. All good!
9	Treatment A - Low dose 400 IU	5	Happy to help.	5	
10	Treatment B - High dose 3200/800 IU	4	Happy to help any research.	3	most of the time yes except felt bad after second dose.
11	Treatment A - Low dose 400 IU	3		4	
12	Treatment A - Low dose 400 IU	4	Easy to take part, not too much work	4	
13	Treatment B - High dose 3200/800 IU	5	I would be more than happy to take part in another study	5	When I had an issue, it was quickly attended to and I was well reassured by the team.
14	Treatment B - High dose 3200/800 IU	5	easy no worries.	5	

*Scores are on a scale of 1 to 5, 1 means ‘strongly disagree’ and 5 means ‘strongly agree’

4.14.2.3 Patient Diaries

The patient representatives within the TSC had predicted that patient diaries would be poorly completed and would be a poor indication of compliance with the treatment. Therefore, lack of completion of diaries was not counted as a protocol deviation and the patient diary was not the main record of compliance of supplementation. Participants were due to have two diaries each during the study period. However,

none of the participants returned both diaries, in Arm A two participants returned one diary each and one participant returned both diaries. In Arm B, four participants returned one diary each and two participants returned both. Some of the returned diaries were not fully completed.

4.14.3 Disease Index

The CDAI was completed as scheduled for all participants who were invited for follow up (Table 4-13). The calculation of the CDAI was shown to be feasible within the study.

Table 4-13 Crohn's Disease Activity Index Scores

	Arm A Cholecalciferol 400 IU			Arm B Cholecalciferol 3,200/ 800 IU		
	Eligibility n (%)	12-week follow-up n (%)	24-week follow-up n (%)	Eligibility n (%)	12-week follow-up n (%)	24-week follow-up n (%)
Total (n)	11	8	6	11	9	5
Indicative of remission (<150)	8 (72.7)	4 (36.4)	4 (36.4)	7 (63.6)	8 (72.7)	4 (36.4)
Mild disease (150-220)	1 (9.1)	1 (9.1)	1 (9.1)	3 (27.3)	1 (9.1)	1 (9.1)
Moderate disease (221-450)	2 (18.2)	3 (27.3)	1 (9.1)	1 (9.1)	0 (0.0)	0 (0.0)
Missing	0 (0.0)	3 (27.3)	5 (45.5)	0 (0.0)	2 (18.2)	6 (54.5)
Mean (SD)	114.2 (108.7)	156.9 (102.2)	116.0 (72.9)	109.2 (86.2)	63.6 (59.2)	105.4 (74.7)
Median (IQR)	106.0 (28-174)	140.0 (76-244)	89.0 (69-159)	92.0 (31-186)	75.0 (10-99)	113.0 (73-142)
Range	5-365	24-311	47-243	12-273	0-163	0-199
Missing (n)	0	3	5	0	2	6

4.14.4 Biochemical Measures

4.14.4.1 Safety

Table 4-14 shows blood test results for corrected calcium, PTH and vitamin D results as 25(OH)D. All patients had a 25(OH)D level of <50nmol/l at eligibility. Levels increased over the trial period in both treatment arms. There were no incidences of vitamin D toxicity over the study period. Corrected calcium remained within the normal range for all participants where this was measured throughout the study. Although PTH was elevated in some participants, a medically trained doctor confirmed that this was not due to hyperparathyroidism.

4.14.4.2 Efficacy

The statistical analysis plan did not include collection of individual blood test values for efficacy blood samples such as CRP. Instead, the presence or absence of inflammation and/or iron deficiency anaemia as indicated by the blood test results was recorded on the CRF to demonstrate the feasibility of collection of samples. Only one person was recorded to have inflammation according to a raised CRP. This was in treatment Arm A at the 12 week follow up appointment. In terms of iron deficiency anaemia, in Arm A one person had anaemia at eligibility according to both FBC and iron studies, and one person at the 12 week follow up according to iron studies. In Arm B, a total of four participants had anaemia according to both FBC and iron studies, one at eligibility, two at the 12 week follow up and one at the 24 week follow up.

Table 4-14 Blood Test Results at Baseline and Follow up

	Arm A Cholecalciferol 400 IU			Arm B Cholecalciferol 3,200/800 IU		
	Baseline	12-week follow-up	24-week follow-up	Baseline	12-week follow-up	24-week follow-up
25(OH) D (nmol/L) (n)	10	8	6	11	9	5
Mean (SD)	29.6 (11.4)	34.6 (15.7)	63.5 (23.1)	23.5 (9.3)	75.2 (25.5)	65.0 (13.6)
Median (IQR)	31.0 (17.0-35.0)	31.0 (26.0-38.5)	70.0 (37.0-76.0)	23.0 (15.0-32.0)	74.0 (66.0-87.0)	66.0 (65.0-68.0)
Range	13.0-48.0	17.0-69.0	35.0-93.0	12.0-38.0	28.0-121.0	44.0-82.0
Missing (n)	1	3	5	0	2	6
Corrected calcium (mmol/L) (n) *Normal range 2.2-2.6*	11	8	6	11	9	5
Mean (SD)	2.3 (0.1)	2.3 (0.1)	2.3 (0.1)	2.3 (0.1)	2.3 (0.1)	2.4 (0.1)
Median (IQR)	2.3 (2.3-2.4)	2.29 (2.28-2.33)	2.3 (2.3-2.4)	2.3 (2.3-2.4)	2.29 (2.27-2.34)	2.37 (2.35-2.38)
Range	2.2-2.4	2.2-2.4	2.2-2.5	2.2-2.5	2.2-2.4	2.2-2.4
Missing (n)	0	3	5	0	2	6
PTH (pmol/L) (n) *Normal range 1.6-7.2*	11	8	6	11	9	5
Mean (SD)	6.9 (3.9)	8.9 (7.4)	5.2 (1.8)	8.2 (2.8)	8.1 (3.3)	6.5 (2.9)
Median (IQR)	6.2 (4.7-8.1)	6.7 (4.5-9.7)	5.4 (3.4-6.8)	7.6 (6.4-10.1)	7.4 (5.8-9.8)	5.8 (5.3-7.7)
Range	2.4-16.7	3.3-26.0	2.9-7.5	5.0-13.8	4.8-14.4	2.9-10.7
Missing (n)	0	3	5	0	2	6

4.14.4.3 Hepcidin

Although blood samples had been collected in the study for hepcidin analysis, in January 2022 BHH laboratories reported that they were no longer able to process these samples. Given that the study and the NIHR funding were closed by this point,

there was no time to source an alternative laboratory. A protocol amendment was made to remove hepcidin from the study and the stored samples destroyed without analysis (protocol V6.0 19/01/2022) (Appendix 6).

4.14.4.4 Vitamin D Metabolites

Vitamin D metabolites were analysed within the University of Birmingham as planned. Although there are multiple metabolites, the CTU database was developed to record the results of only one, 25(OH)D3, as shown in Table 4-15. As no comparative analyses were planned this exercise was primarily effective at demonstrating the feasibility of collecting and processing samples for vitamin D metabolites in the study.

Table 4-15 CTU Analysis of vitamin D Metabolite 25(OH)D3

25(OH)D3 (reference range 20-120nmol/L)	Arm A Cholecalciferol 400 IU			Arm B Cholecalciferol 3,200/800 IU		
	Baseline	12-week follow-up	24-week follow-up	Baseline	12-week follow-up	24-week follow-up
Total (n)	10	7	4	11	8	5
Missing (n)	1	4	7	0	3	6
Mean (SD)	29.7 (11.8)	34.2 (18.9)	68.5 (14.7)	22.9 (13.4)	60.3 (23.8)	58.7 (16.2)
Median (IQR)	31.6 (23.4-40.2)	32.9 (23.5-35.4)	67.1 (57.7-79.4)	16.5 (12.0-28.7)	68.2 (45.7-74.1)	56.8 (55.0-67.5)
Range	10.9-46.7	15.4-73.8	52.6-87.3	10.6-53.1	21.4-85.4	35.4-79.0

Results for the remaining vitamin D metabolites, presented by University of Birmingham laboratories, are shown in Table 4-16. The remaining metabolites in include 25OHD3 Total, 25OHD2, 3-Epi-25OHD3, and 24,25(OH)2D3.

Table 4-16 Results for 25OHD3 Total, 25OHD2, 3-Epi-25OHD3, and 24,25(OH)2D3

	Arm A Cholecalciferol 400 IU			Arm B Cholecalciferol 3,200/800 IU		
	Baseline	12-week follow-up	24-week follow-up	Baseline	12-week follow-up	24-week follow-up
25OHD3 Total (reference range 10-250 nmol/L)						
Mean (SD)	32.1 (11.7)	36.6 (18.0)	69.7 (12.6)	25.4 (12.3)	63.4 (21.2)	55.0 (11.2
Median (IQR)	33.1 (28.3-43.4)	34.3 (25.8-38.8)	68 (63.6-72.4)	18.5 (14.9 - 35.0)	70.2 (67.4-77.4)	56.9 (55.9-57.9)
Range	12.2-50.6	16.5-75.2	54.1-88.3	12.7-54.0	24.9-85.8	37.4-68.7
25OHD2 (reference range 0.4-4.5 nmol/L)						
Mean (SD)	2.5 (1.2)	2.4 (1.5)	1.1 (0.3)	2.5 (1.8)	1.0 (0.9)	1.3 (0.4)
Median (IQR)	2.1 (1.6-3.3)	1.5 (1.2-3.8)	1.1 (1.0)	2.05 (0.8-3.2)	0.73 (0.4-1.0)	1.17 (1.1-1.2)
Range	1.4-5.0	1.1-5.4	0.9-1.6	0.5-7.0	0.3-3.4	0.9-2.0
3-Epi-25OHD3 (reference range 0.5-18 nmol/L)						
Mean (SD)	1.1 (0.6)	1.4 (1.2)	4.0 (1.9)	0.7 (0.4)	2.3 (0.9)	2.4 (0.5)
Median (IQR)	1.2 (0.8-1.6)	0.7 (0.6-1.3)	3.5 (3.2-3.8)	0.6 (0.4-0.9)	2.2 (1.5-3.2)	2.6 (2.5-2.6)
Range	0.1-2.1	0.6-4.1	1.8-7.0	0.2-1.8	0.8-3.8	1.4-2.9
24,25(OH)2D3 (reference range 0.001-30 nmol/L)						
Mean (SD)	1.61 (0.9)	1.92 (1.6)	4.45 (1.4)	1.0 (1.0)	3.9 (1.9)	3.6 (1.0)
Median (IQR)	1.65 (1.0-2.0)	1.57 (1.1-1.6)	3.81 (3.4-3.5)	0.7 (0.3-1.2)	3.6 (3.2-4.7)	4.0 (3.9-4.0)
Range	0.22-3.46	0.78-5.84	3.36-6.84	0.1-3.9	0.9-7.3	1.9-4.6

Data in Table 4-14 show serum 25(OH)D data that were analysed by a hospital-based laboratory using a chemiluminescent immunoassay methodology (Bikle, 2018). This is distinct from the laboratory methods used to derive the serum 25(OH)D values shown in Figure 4-5.

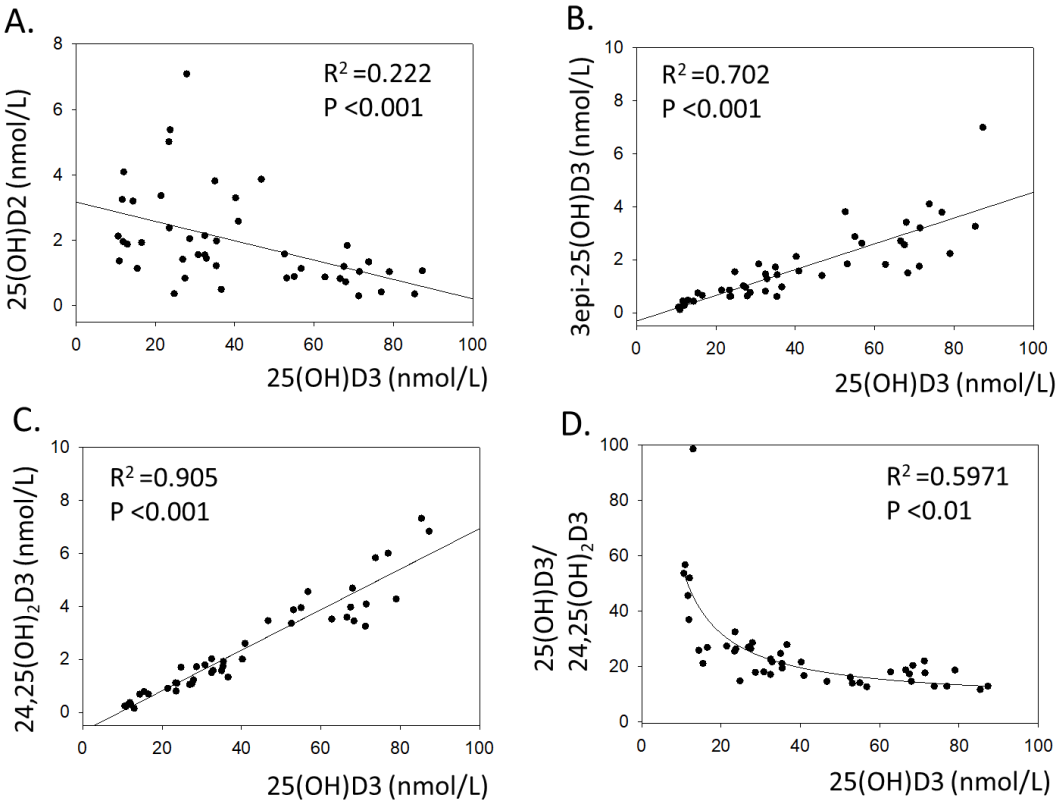


Figure 4-5 Relationship between serum vitamin D metabolites in Crohn's disease patients. Combined data for all patients at different time points showing the relationship between serum 25-hydroxyvitamin D3 (25(OH)D3) with (A) serum 25(OH)D2, (B) 3epi-25(OH)D3 and (C) 24,25-dihydroxyvitamin D3 (24,25$(OH)_2$D3). The relationship between serum 25(OH)D3 and the ratio of 25(OH)D3/24,25(OH)D3 is shown in (D). Linear regression analyses are shown as R^2 values, with associated *p* values.

Comparison between these analyses confirmed that treatment Arm B (3,200 IU vitamin D/day) was sufficient to significantly elevate serum 25(OH)D values by the 12-week follow-up, with no further increase after 24 weeks. By contrast, in treatment Arm A, 400 IU vitamin D/day had no effect at week 12 but showed elevation of serum 25(OH)D at week 24. Collectively, the data in Table 4-15 and Table 4-16 suggest that supplementation with 400 IU/day vitamin D is sufficient to raise serum 25(OH)D values in Crohn's patients if this is viewed in a longer-term perspective.

The inclusion of measurements of 3epi-25(OH)D3, 24,25$(OH)_2$D3 and 25(OH)D2 provide a further insight into the metabolic changes associated with either low dose (400 IU/day) or high dose (3,200 IU/day) vitamin D. Notably, serum levels of 24,25$(OH)_2$D3 and 3-epi-25(OH)D3 paralleled the changes in serum 25(OH)D3, indicating that the 3,200 IU/day dose of vitamin D supplementation more rapidly induced catabolic inactivation of 25(OH)D3, whilst also showing that 400 IU/day vitamin D was still able to promote a catabolic response, albeit at a later time point. Nevertheless, it is still important to recognise the advantage of the higher dose supplementation, as this was still able to maintain elevated levels of serum 25(OH)D3, despite induction of catabolism much earlier than low dose supplementation.

4.14.5 Faecal calprotectin

Faecal calprotectin results are shown in Table 4-17. Collection of stool samples for faecal calprotectin was problematic with several missing samples even in those participants who attended their follow up, hence any interpretation of these results is problematic.

Table 4-17 Faecal Calprotectin Results

	Arm A Cholecalciferol 400 IU		Arm B Cholecalciferol 3,200/800 IU	
	Eligibility	24-week follow-up	Eligibility	24-week follow-up
Total (n)	4	3	3	2
Missing samples (n)	7	8	8	9
Range µ/g*	20.0-104.0	41.0-1251.0	33.0-409.0	20.0-1086.0

*<50 µ/g to 100 µ/g quiescent disease, >100 µ/g to 250 µ/g inflammation is possible and >250 µ/g active inflammation is likely

4.15 Compliance with the vitamin D supplement

In total eight participants prematurely stopped taking their vitamin D supplement. In five participants this was because of the COVID-19 pandemic in 2020 preventing study follow up and provision of further supplies of vitamin D for a period. The remaining three participants chose to stop taking the vitamin D as they perceived it had caused an Adverse Event (AE). The doctor agreed with stopping the vitamin D supplement in only one of these AE's. Participants who had stopped taking their vitamin D remained in the study and completed study follow up as per the protocol.

The patient diaries and count of returned unused vitamin D supplements were not a successful strategy for calculating compliance, as very few were returned. The participant indication of compliance, as recorded on the CRF at follow up appears to be the most reliable method of data collection related to compliance in this study. Figure 4-6 shows participant reported compliance with the vitamin D supplement by treatment arm for all participants who were invited to a 12 and 24 week follow up appointment. Most participants had taken all/most of their vitamin D supplements at both timepoints. Overall, there is missing data for five participants at 12 weeks and 11 participants at 24 weeks.

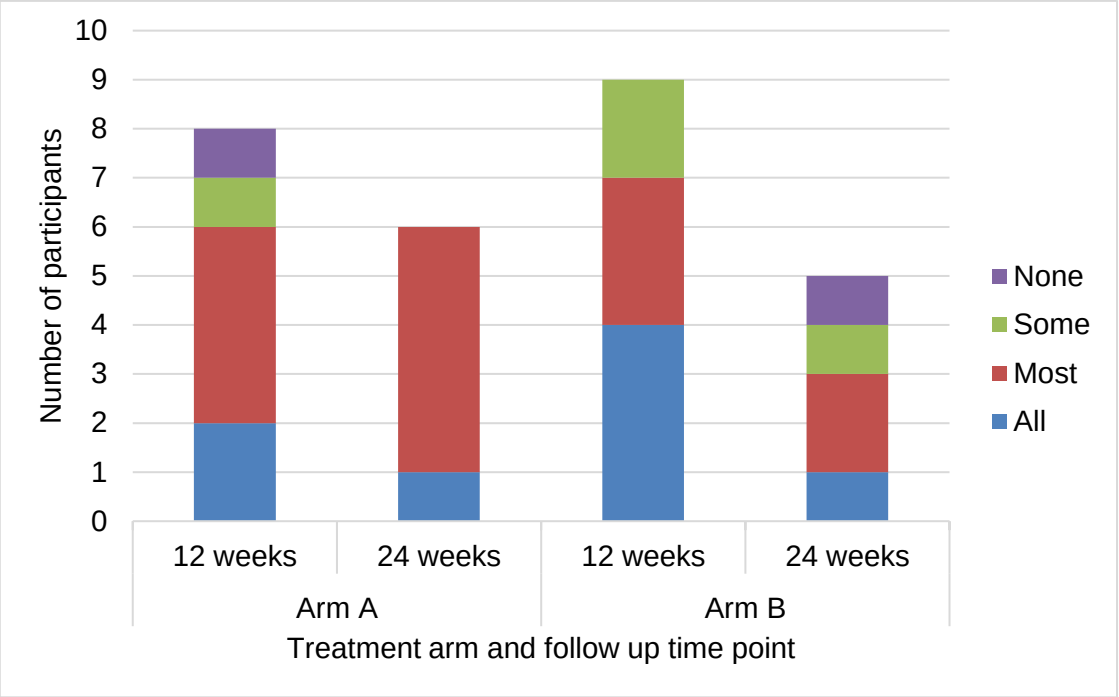


Figure 4-6: Participant reported compliance with vitamin D. Data includes patient reported intake at the 12 week and 24 week follow up appointments. Most patients reported taking all or most of their vitamin D. Where participants reported taking none, this was due to an adverse event and is recorded in premature discontinuation of the vitamin D. There is missing data in five participants at week 12, and 11 participants at week 24 due to the impact of the COVID-19 pandemic.

4.14.6 Diet and Lifestyle Questions at 28 weeks

A total of 15 participants had a 28 week follow up appointment. No comparative analysis has been carried out between participant's reported modifiable risk factors from the original observational study to 28 weeks. However, descriptively findings are like that reported in the screening study (section 3.9) with no obvious changes in reported lifestyle habits.

Table 4-18 shows the data on sun exposure.

Table 4-18 Reported Sun Exposure at Baseline and 28 weeks

Reported sun exposure	Arm A Cholecalciferol 400 IU	Arm B Cholecalciferol 3,200/800 IU	Arm A Cholecalciferol 400 IU	Arm B Cholecalciferol 3,200/800 IU
	*Baseline n = 22 (%)		28 Weeks n = 15 (%)	
Has the patient visited a warm/sunny country in the preceding three months?				
Yes	-	2 (18.2)	-	-
No	11 (100)	9 (81.8)	8 (100)	7 (100)
If the patient is exposed to sunshine does their skin normally…				
tan or darken easily?	5 (45.5)	6 (54.5)	5 (52.5)	3 (42.8)
go red then tan?	3 (27.3)	3 (27.3)	1 (12.5)	-
burn?	3 (27.3)	2 (18.2)	2 (25.0)	4 (57.2)
Would the patient normally use a sun lotion with sun protection factor (SPF) if they are exposed to sunshine?				
Yes	9 (81.8)	10 (90.9)	5 (62.5)	7 (100)
No	2 (18.2	1 (9.1)	3 (37.5)	-
What SPF would they normally use?				
Mean (SD)	36.9 (11)	37.2 (17.3)	38	43
Median (IQR)	30 (30-50)	50 (30-50)	30	50
Range	25-50	5-50	30-50	20-50
Unknown	3 (27.3)	2 (18.2)	-	-
In the sunshine is the patient most likely to wear…				
Shorts and a short-sleeve top	6 (54.5)	6 (54.5)	7 (87.5)	5 (71.4)
Long trousers or skirt and a short-sleeve top	2 (18.2)	3 (27.3)	1 (12.5)	2 (28.6)
Keep arms and legs covered	3 (27.3 %)	1 (9.1 %)	-	-
Keep whole body covered	-	1 (9.1 %)	-	-

*Baseline data is that reported by participants when they were in the screening study. SPF could also be shown as categorical data but was analysed as continuous data within the CTU statistical analysis plan.

Table 4-19 shows a comparison of the consumption of vitamin D containing foods.

At baseline, only three out of 22 participants reported that they were current smokers.

At the 28 week follow up all those attending were non-smokers.

Table 4-19 Reported Weekly Consumption of Vitamin D Containing Foods at Baseline and 28 Weeks

Weekly Consumption of vitamin D containing foods	Arm A Cholecalciferol 400 IU	Arm B Cholecalciferol 3,200/800 IU	Arm A Cholecalciferol 400 IU	Arm B Cholecalciferol 3,200/800 IU
	***Baseline** n = 22 (%)		**28 Weeks** n = 15 (%)	
Oily fish (salmon, sardines, herring, mackerel)				
0 (rarely or never)	5 (45.5)	4 (36.4)	4 (50)	4 (57.2)
1-2 times	6 (54.5)	6 (54.5)	4 (50)	3 (42.8)
3-4 times	-	1 (9.1)	-	-
Red meat				
0 (rarely or never)	3 (27.3)	4 (36.4)	2 (25)	3 (42.8)
1-2 times	5 (45.5)	6 (54.5)	5 (62.5)	1 (14.3)
3-4 times	2 (18.2)	1 (9.1)	1 (12.5)	2 (28.6)
5+ times	1 (9.1)	-	-	1 (14.3)
Liver or offal				
0 (rarely or never)	11 (100)	10 (90.9)	8 (100)	7 (100)
1-2 times	-	1 (9.1)	-	-
Eggs including the yolk				
0 (rarely or never)	2 (18.2)	1 (9.1)	2 (25)	1 (14.3)
1-2 times	6 (54.5)	5 (45.5)	3 (37.5)	5 (71.4)
3-4 times	3 (27.3)	2 (18.2)	2 (25)	1 (14.3)
5+ times	-	3 (27.3)	1 (12.5)	-
Foods that are labelled as fortified with vitamin D (breakfast cereal, spread, etc.)				
0 (rarely or never)	10 (90.9)	10 (90.9)	4 (50)	6 (85.7)
1-2 times	0	1 (9.1)	1 (12.5)	1 (14.3)
3-4 times	-	-	1 (12.5)	-
5+ times	1 (9.1)	-	2 (25)	-

*Baseline data is that reported by participants when they were in the observational study. Percentages shown are a percentage of the number of participants where data were collected, not the sample as a whole.

4.14.6.1 Use of vitamin D containing supplements at 28 weeks

At the 28 week follow up, 62.5% (n=5) of participants in Arm A and 14.2% (n=1) of participants in Arm B reported that they had continued to take a vitamin D containing supplement past the end of the trial. In Arm A, two participants did not know the dose of vitamin D, with the three remaining participants taking a median 800IU vitamin D

dose (range 400IU – 1000IU). In Arm B the one participant who reported continuing a vitamin D supplement was taking an 800IU dose.

4.14.7 Protocol deviations

Table 4-20 shows the summary of protocol deviations. Eighteen participants (81.8%) had at least one protocol deviation. Thirteen (59.1%) had at least one major deviation and 18 (81.8%) at least one minor deviation. The large number of deviations are due to the first wave of COVID-19 interrupting and halting patient follow up. So, uncollected data is counted as a protocol deviation here in addition to missing data. The premature discontinuation of the study treatment includes participants who were not invited to their 12 week follow up appointment due to COVID-19, and so were not given a further supply of vitamin D as planned.

Table 4-20 Summary of Protocol Deviations

Protocol deviation	Minor/major	Arm A Cholecalciferol 400 IU n (%)	Arm B Cholecalciferol 3,200/800 IU n (%)	Total n (%)
Stool samples not taken or not sent/ analysed	*Minor*	8 (72.7)	9 (81.8)	17 (77.3)
Blood samples not taken or not sent/ analysed	*Major*	6 (54.5)	7 (63.6)	13 (59.1)
PROM not completed	*Minor*	5 (45.5)	7 (63.6)	12 (54.5)
Patient stops treatment prematurely	*Minor*	4 (36.4)	4 (36.4)	8 (72.8)

PROM = patient reported outcome measure

4.15 Adverse Events (AE)

Data on all AEs were collected for the study except those directly related to the patient's CD. No serious adverse events (SAEs) occurred during the study. Table 4-21 shows the reported non-serious adverse events. AEs were evenly distributed across the two treatment arms, with a total of eight AEs reported in six participants. All AEs were classified as mild in severity with only three AEs determined to be related to the vitamin D supplement to some degree. This was 'probably' (n = 1 Arm A, n = 1 Arm B) and 'almost certainly' (n = 1 Arm B) related. Related AEs determine possible causation for the feasibility assessment. Therefore, in terms of feasibility only 3/22 (13.6%) participants reported a causative AE.

Table 4-21 Adverse Events

Adverse Event description*	Arm A Cholecalciferol 400 IU		Arm B Cholecalciferol 3,200/800 IU		Total number of events
	Events n	Patients n (%)	Events n	Patients n (%)	
Groin cyst	1	1 (9.1)	0		1
Tooth infection/root canal	1	1 (9.1)	0		1
Watery Diarrhoea	1**	1 (9.1)	0		1
Nausea	0		1**	1 (9.1)	1
Rash	0		1**	1 (9.1)	1
Sinus infection	0		1	1 (9.1)	1
Throat infection	0		1	1 (9.1)	1
Tooth infection	1	1 (9.1)	0		1
Total	4	4 (36.4)	4	4 (36.4)	8

AEs occurred in 6 participants with 2 participants experiencing 2 AEs each. *All recorded adverse events were non-serious. ** Denotes a related AE

4.16 Feasibility outcome assessment summary

Table 4-22 details the feasibility assessment based on the results and taking in to account mitigating factors such as the impact of the COVID-19 pandemic on the study. Overall, it is reasonable to deem the study feasible with modifications.

Table 4-22 Feasibility Assessment

Outcome target as per the protocol	Achieved	Comment
At least 50% of all eligible patients could be consented	47.1% consent rate	6% of eligible patients were not approached due to the Sponsor temporary halt in January 2020. Delays in approval of an amendment prevented consent of a further 2 participants.
At least 80% participant compliance with the intervention	This is difficult to assess due to missing data.	The majority of participants reported take all or most of the vitamin D.
Retention and follow up in at least 80% of all recruited participants at six months (24 weeks)	There were no withdrawals from the study, so the study achieved full retention. 50% had a 24 week follow up appointment. 68% had a 28 week follow up appointment.	No participants withdrew from the study. However, COVID-19 pandemic prevented a 6 month (24 week) follow up appointment in 50% of participants during 2020.
Completion of all trial processes in at least 80% of participants.	Not achieved, modifications required to ensure stool samples are collected. Patient diaries were unsuccessful.	COVID-19 pandemic prevented completion of trial processes and collection of data in several participants.
Absence of adverse reactions and causative adverse events in at least 80% of participants	Achieved, only 13.6% of patients reported a causative adverse event/ reaction	No modifications required for a future trial in this respect

4.16.1 Critique of clinical trials as a methodology

Well-designed RCTs have long been considered the gold standard in providing definitive, unbiased evidence of treatment effect. However, there are distinct limitations in RCT methodology that render it unsuitable for many treatments. Kao et al (2008) describe how research reports in surgery are rarely RCTs, with surgical treatments only half as likely to be based on RCT evidence compared to medicine. This is partly due to practical problems raised by the nature of RCTs including the

difficulty of randomising and/or blinding during surgical procedures. Kao et al (2008) further describe challenges to the use of RCTS in rare diseases and oncology studies where large numbers are required to show a treatment effect. Vitamin D trials have been criticised for being particularly open to bias due to selection of non-deficient patients, effects of diet and sun exposure and the fact that participants have easy access to additional vitamin D supplements, all being confounding factors in interpretation of data (Scragg, 2018). Nevertheless, if these factors are recognised at the design phase, RCTs can still be useful in vitamin D research. There are several factors that continue to affect the applicability of results including trial effect, participant selection, and participant effects.

Trial Effect

Where RCTs have been rigorously designed to prevent bias, studies have suggested that the nature of the RCT might in fact introduce bias via the 'trial effect' as described by Braunholtz et al (2001). The trial effect may include elements such that patients feel better just from being included in a research study or from the additional attention and observation they receive as a participant in research. The authors conclude that, although the evidence is poor, in a systematic review of 21 studies there is a suggestion of impact from the trial effect. It is important that these human factors are recognised.

Other positive bias effects of an RCT include an enhanced level of expert care from experienced clinicians involved in research. Hallstrom et al (2003) report analysis of the AVID and CAST trials in treatments for cardiac arrythmia. In CAST the treatment intervention was found to be harmful, and the study was discontinued. Despite this,

participation in CAST was associated with a 20% reduction in risk of mortality compared to non-participation. Furthermore, Hallstrom et al (2003) report that in AVID, the intervention was found to confer no harm or benefit but, despite this, non-participation was associated with a higher mortality rate. Although they cannot conclude causation, the suggestion is that overall, research participants benefited from the care of experts in the field, regardless of the intervention under investigation. The inclusion of a control group in trial design helps to account for any change that is due to being part of a trial.

In D-CODE the trial effect is unlikely to impact on measurable clinical parameters, such as biochemistry and reports of symptoms. Apart from the provision of a vitamin D supplement participants did not receive any additional specialist care and their CD management was as per normal clinical care.

Selection Effect

One key element of RCT design is elimination of confounding factors, focusing treatment effect on the intervention alone, excluding any external influencers to explain how and why an intervention works under ideal conditions (Sacristán and Dilla, 2018). Selection bias is reduced using randomisation with or without blinding. However, it must be recognised that the inclusion and exclusion criteria of participants in a RCT presents its own form of selection effect that may bias results or the generalisability of results. Lung cancer is a disease of the elderly with just over half of new cases being diagnosed in those aged over 70 years. However, in a review of 419 ongoing clinical trials in lung cancer, Schulkes et al (2016) found that 88% of trials implicitly or explicitly excluded elderly people and those with co-morbidities from

participation. They report that 2% of trials were designed for the elderly but only accepted participants who were deemed as ‘fit’ by performance indicators. The rationale for excluding older, more frail participants is that the results of RCTs are likely to be less positive when these older patients are included or will be inconclusive due to smaller treatment effects. This then brings in to question how the results of these trials can be extrapolated to the elderly, frail population, being the primary recipient of interventions in clinical practice.

Mol et al (2013) compared survival outcomes for patients with colo-rectal cancer participating in the CAIRO chemotherapy study and those that did not participate. Non-participants received treatment outside of the CAIRO trial and were separated into those who met and those that did not meet the inclusion criteria for participation in CAIRO. The authors found that non-participants who met the inclusion criteria had similar survival outcomes to participants in the CAIRO trial (15.7 and 17.0 months). However, those who did not meet the inclusion criteria had a much poorer survival outcome (9.3 months). This suggests that if patients in clinical practice have similar characteristics to participants in a trial, outcomes will be similar. However, in a broader more diverse patient population who do not meet the same criteria, trial treatments are unlikely to offer equal effect. Thus, results from a rigorously controlled trial cannot always be extrapolated to a more general, co-morbid population who are often the main recipients of treatment.

In D-CODE these effects were minimised by having no upper age limit. Participants were only excluded where they had a co-morbidity (such as kidney stones or existing hypercalcaemia) that would make vitamin D supplementation problematic. In addition, participants were excluded who were taking medications, that are not

commonly used in CD, that may impact on vitamin D levels as per the vitamin D SmPC. The aim in a future trial would be to keep exclusion criteria to a minimum to ensure a diverse representation of patients.

Participant Effect

The challenge of adequate recruitment in to RCTs is well recognised (Bertram et al., 2019). Where the range and number of potential participants in a RCT is narrowed by study inclusion/exclusion criteria; the range and number of those recruited is further narrowed by participant factors.

In a cross-sectional study of 200 orthopaedic patients, Hollis and Davis (2018) explored reasons for patients agreeing or not agreeing to participate in trials. They found that 84% of patients in principle would be happy to take part in a trial, with 58% citing ‘benefit to patients in the future’ as a reason to participate. The main reasons identified for possibly declining participation were travelling distance (n=94), lack of information (n=90), extra scans (n=76) and time inconvenience (n=74).

In a review of cancer trials, Bell and Balneaves (2015) found that 28% of trials reported time inconvenience and travelling distance as barriers to participation and 25% of trials reported fear of randomisation as a barrier. Altruism is a key influencing factor for participation in a trial as has been shown in other studies (Fearn et al., 2010, Nielsen and Berthelsen, 2019). In mapping facilitators and barriers to patient participation, a recent review of 26 systematic reviews, including 429 primary studies, identified similar facilitators and barriers to patient participation (Sheridan et al., 2020).

Thus, recruited participants in trials will often be people who are:

- interested in taking part in research and ‘giving something back’
- can travel for additional study visits (access to a car or reliable public transport)
- can commit time for additional study visits/prolonged appointment times
- can manage the burden of additional treatments or interventions

It is reasonable to suggest then that RCT participants are unlikely to be entirely representative of the general population with a similar condition in clinical practice. Thus, in D-CODE the COVID-19 management strategies would be a useful addition to any future trial in allowing remote follow up and posting of study supplies to reduce travel and the burden of other study procedures.

Pragmatic trials

Pragmatic clinical trials offer an alternative to traditional RCTs, in which treatments and interventions can be investigated in real world settings (Meinecke et al., 2017). Including a wider more heterogenous representation of the patient population adds to the ‘external validity’ or generalisability of the results (Sacristán and Dilla, 2018). Nevertheless, Sacristán and Dilla (2018) stress that, while attempting to represent the average patient, this heterogenity may dilute treatment effect and make it difficult for clinicians to determine beneficial effects in individuals.

Reducing the burden of study visits and other trial elements to participants is a further consideration in pragmatic trials (Ford and Norrie, 2016). The PRECIS-2 tool was developed to help trial designers identify elements of their trial and determine how similar processes were to, for example, normal clinical care which would be considered a pragmatic attitude (Loudon et al., 2015). In total 9 domains are covered in the PRECIS-2 tool including:

- Delivery flexibility —How different is the flexibility in how the trial intervention is delivered and the flexibility expected in usual clinical care?
- Follow-up—How different is the intensity and flexibilty of follow-up of participants from the typical follow-up in usual clinical care?

Where trials are designed to run in accordance with usual clinical care there is still a question over how truly flexible and pragmatic they are. In terms of follow up, patients may reasonably expect to be able to cancel planned clinical appointments and re-organise these to a more convenient time when needed. However, within a trial this may prove to be a challenge, where follow up is required to take place within pre-defined time periods. Clinical appointments may not need to be carried out as regularly as trial appointments, particularly in those patients who are deemed to be clinically stable. So, mirroring clinical care may not be feasible.

Furthermore, patients may reasonably expect to be able to return to carry out a clinical procedure, such as a blood test, on a day other than their booked clinic appointment. In a trial this may not be appropriate. For example, within D-CODE two key follow up appointments were due at 12 and 24 weeks (+/- 2 weeks) with study procedures scheduled for each face-to-face visit. Visits outside of these windows or missed study procedures at these visits, for any reason, would have been considered protocol deviations with the CTU using dates to validate processes. The introduction of remote follow up and off-site blood tests in the COVID-19 amendment allowed greater flexibility for participants, and a recognition that there was not impact on safety or data integrity if study procedures were carried out on slightly different days. This will be a useful strategy in any future study.

The serious breach mentioned earlier occurred due to attempts to make the trial processes flexible and more convenient for participants, as would occur in normal clinical care. The Sponsor was keen that we aimed to deliver the project within 'the real world' and in principle agreed to several suggested changes to facilitate this, such as routine posting of vitamin D supplements and postal questionnaires to reduce the need for some of the face-to-face appointments. However, the CTU would not agree to these due to concerns over the ability to monitor processes. The substantial amendment to the protocol that followed the serious breach clarified and strengthened some of the restrictions within the protocol, but it did little to increase the flexibility of processes. The only real concession was the change of the final appointment to a telephone/postal follow up to reduce the travel burden to participants.

Ultimately, the pragmatic changes introduced by Health Research Authority (HRA), REC and MHRA in response to the COVID-19 pandemic finally allowed some of the flexibility the trial needed. The proposed COVID-19 management measures demonstrated that it was possible to deliver D-CODE in a different, more pragmatic way that still maintained safety. There is enthusiasm for new ways of working to be adopted in the management of clinical trials going forward (Doherty et al., 2020, Apostolaros et al., 2020). It is not clear if HRA and MHRA will retain any of the temporary measures they put in place following the COVID-19 pandemic, but it must surely be time for them to review their processes and determine if there is a more pragmatic way to routinely conduct minimal risk trials in the future.

4.17 Discussion

The aim of this study was to assess the feasibility of conducting a national, multi-site RCT in adults with CD and identified vitamin D deficiency. The measures of feasibility for the study include consent rate, retention, compliance with vitamin D supplement, completion of study processes, and adverse events. Given the issues with site opening and the impact of the COVID-19 pandemic it is appropriate to determine that the study was completed successfully and is feasible with modifications. The different components of the project will be explored, culminating in a discussion of proposed modifications for a future study. The secondary aim of the study was to investigate the role of the CTU in a hybrid study with the researcher carrying out trial co-ordination. The success of this approach will be explored.

This discussion relates to the feasibility clinical trial, however, the relevant PPI aspects of the study have been described and discussed in previous sections in the screening study, as it relates to both studies (sections 3.3.3 to 3.3.3.4 and 3.10.8) .

4.17.1 Sample size and Recruitment

The purpose of identifying three hospital sites for D-CODE was to demonstrate the feasibility of recruitment in a larger, multi-centre trial. The failure to open at more than one site, even though all proposed sites were within the same NHS Trust, was disappointing. Although physician engagement is recognised as a crucial element in ensuring active patient recruitment in trials (Fletcher et al., 2012, Stock et al., 2015), there are other practical considerations within a study that physicians are unlikely to be involved in. Physicians at the three hospital sites were supportive of the study but were not involved in arranging clinic rooms for example. These can be described as administrative barriers hindering opening of the study at other hospital sites, that could be overcome by JF within her own hospital setting, but over which she had no

influence at other hospital sites. A systematic review of challenges in nurse-led RCTs found that lack of administrative support and organisational barriers were common problems (Vedelø and Lomborg, 2011). While there are moves to encourage nurse led research and RCTs (Gullick and West, 2016, Munday et al., 2020), it must be recognised that nurse led research requires the same level of practical, administrative, and organisational support as physician led studies to be successful. Thus, it is not possible to assess recruitment within D-CODE as a multi-site study and recruitment data is presented for a single centre. Despite this, it was still possible to assess the feasibility of study processes and participant compliance within one site.

Informing the patient's G.P. of their vitamin D result from the observational screening study had some additional impact on recruitment for the feasibility clinical trial. A number of G.Ps were proactive in offering treatment to those who were found to have vitamin D deficiency in the screening study, which meant they were not eligible for the trial. This would be an important consideration in identifying any potential participants in a future trial and may be mitigated by informing G.Ps of screening results after patients have considered participation in the trial.

A formal sample size calculation may not be appropriate for feasibility studies and so rule of thumb estimates are often recommended (Billingham et al., 2013). However, there is a wide range of recommendations (Lancaster et al., 2004, Julious, 2005, Sim and Lewis, 2012). Target sample size for the D-CODE vitamin D supplementation trial was at the higher end given the initial aim to recruit to three sites. However, given the practical time constraints of being a lone investigator and carrying out all trial management within the research, a target at the lower end of the range would have

been a more realistic goal. With only one site opening and multiple delays, it was not possible to reach the full target recruitment of 50 within the study period. Nevertheless, 24 patients were consented, and 22 participants were randomised from QEHB site alone. This exceeded the target for recruitment set for QEHB as a single site and is still within the parameters of other feasibility studies registered with the United Kingdom Clinical Research Network (UKCRN). In a review of 76 clinical trials registered with the UKCRN, Billingham et al (2013) report studies with sample sizes of 10 participants per arm for feasibility studies and eight per arm for pilot studies. A sample size of 20 (10 per arm) has been reported in published feasibility studies (Trevelyan et al., 2016). Thus, although below the overall target, the sample size achieved in D-CODE is adequate.

Poor recruitment in RCTs is recognised as a frequent problem, with approximately 50% of RCTs failing to recruit to target (Fletcher et al., 2012) and 19% of studies either terminating or continuing with less than 85% of target recruitment (Carlisle et al., 2014). A consent rate of 47.1% was reported in the current study, just below the required 50% consent rate for the feasibility assessment. In the 'not consented' section of Table 4-7, six patients are included who were no longer eligible. This was due to the G.P. of three patients prescribing vitamin D supplementation once they were identified as vitamin D deficient in the screening study. Receipt of a prescribed vitamin D supplement was one of the exclusion criteria and this meant that they were no longer eligible to join the study, as a prescribed medication could not be stopped for the trial. Clearer communication with the G.P. may have prevented this. The letter with the vitamin D result sent to both the patient and G.P. did not give clear instructions regarding avoiding the prescribing, or purchase, of vitamin D

supplements once they were identified as deficient. In future, a separate letter for those who may be eligible for the trial would need to provide clear information regarding this.

Three patients had their vitamin D re-checked in clinical care following the screening study and were found to have a vitamin D of >50nmol/L at that point, meaning that they were no longer eligible for the feasibility trial. Variances in the results of vitamin D analysis carried out at different laboratories has been discussed (section 4.9.2.1). Had patients been consented to join the trial, when their vitamin D was re-checked at baseline it is likely that they still would have had a vitamin D of >50nmol/L. However, as the re-check took place in clinical care rather than the trial this affected the consent rate shown in Table 4-4. If these six patients are correctly counted as not eligible, rather than not consented, the consent rate would be marginally higher. In addition, two participants included in 'not consented' were in fact not recruited due to a delay in gaining a protocol amendment.

There were multiple contributory factors affecting the consent rate, but the Sponsor temporary halt of the study in January 2020, due to the identified serious breach, and the pause due to the COVID-19 pandemic were key issues. In addition, the study was halted at one point during the key winter months in which vitamin D deficiency is likely to be most prevalent. Although seasonal effect on vitamin D was not a formal outcome in the study, it would have been beneficial in developing an overall recruitment strategy. Prevalence of vitamin D deficiency in the spring and summer may have informed a later study by determining if adequate recruitment would be possible over a longer period beyond the winter months. It is difficult to fully assess

the consent rate but with these mitigating factors it is fair to estimate that the study could have achieved at least 50% consent rate.

4.17.1.1 Serious Breach

Part of the role of the CTU is to ensure that the study is being conducted strictly according to the processes laid out in the study protocol. Any processes that deviate from the protocol are protocol deviations, which may be minor or major deviations. In January 2020 the CTU identified that some processes had been carried out in the initial stages of the study that were not strictly within the protocol or timescales set out in the protocol. These occurred as some participants seen in the Gastroenterology outpatient clinic found it difficult to return to the hospital for appointments, that were closely spaced within the study timeline, due to work and other commitments. An attempt was made to assist patients by posting the vitamin D supplement or allowing a couple of patients to complete their questionnaires on a different day where they could not return to the hospital. All of these were minor deviations that did not affect patient safety in any way or the integrity of the study. However, the CTU identified nine issues that they were not happy with and decided that these should be reported to Sponsor in a potential serious breach report.

The MHRA (2019) definition of a serious breach of GCP is a breach of the research protocol that is likely to affect to a significant degree the safety or physical or mental integrity of the participants; or the scientific value of the trial. JF disagreed with the CTU's assessment of each of the minor protocol deviations and any potential impact they could have had. Indeed, the CTU recognised that there was in fact no impact

from any of them. However, given the number of minor deviations, Sponsor determined that this should be reported to MHRA as a serious breach.

The Sponsor recognised that the protocol required amendment to allow some flexibility and enable patients to comply with the processes. However, from January 2020, while protocol amendments were being made the Sponsor temporarily halted recruitment to the study, while allowing follow up for existing patients in the trial. Protocol version 4.0 04/3/2020 was approved in March 2020. However, by this point the COVID-19 pandemic was affecting the UK. The severe impact that these minor deviations had on the study were a key learning point. Thus, development of any future studies must make processes as patient friendly as possible from the outset.

4.17.2 Retention

There were no participant withdrawals from the study, thus, retention was excellent. The COVID-19 study suspension in April 2020 prevented the initial 11 participants from having follow up appointments during the first national lockdown. However, these participants were not withdrawn from the study and were requested to report any adverse events for the duration of their participation, although for the majority of these no other data was actively requested or collected. The patient experience questionnaire suggested that, overall, participants had a good experience and found taking part in the study easy. This may have contributed to successful retention, even in those who stopped taking their vitamin D due to adverse events.

4.17.2.1 Participant Experience

Of the participants where data was collected 12 out of 14 participants agreed/strongly agreed they would be happy to take part in research again and, 13 out of 14

agreed/strongly agreed that they had a good experience. Although this is a small sample size, the results are reassuring and in accordance with previous survey results from the NIHR Clinical Research Networks. In the report of the 2017/2018 patient experience survey, 83.4% of respondents (n=4312) agreed/strongly agreed that they would take part in research again and 87% agreed/strongly agreed that they had had a good experience (Clinical Research Network Co-Ordinating Centre, 2019). Free text comments from the participant experience PROM suggests that overall, the study was well received from a participant's point of view.

4.17.3 Compliance with Vitamin D supplement

Three different measures of compliance with the vitamin D supplement were tested in this study. Firstly, a pill count of returned and unused vitamin D supplements against the number dispensed, secondly a patient diary and thirdly a verbal report from patients of compliance. The pill count is not reported within the study analysis by the CTU, however so few patients returned unused vitamin D supplements, even when a pre-paid envelope was provided, that this was not a successful strategy. Patient diaries were very poorly completed, with only a few returned and often not complete. PPI had predicted this outcome at the start of the study, so although anticipated, it was useful to test this in the feasibility study. Clearly, in terms of assessing compliance with the vitamin D supplement, the patient diaries were not expected to be a reliable indicator. It is unclear if electronic diaries would have been more successful. A large rheumatoid arthritis clinical trial showed 94% participant compliance with a daily electronic diary (Bingham et al., 2019) so it would be important to consider this with the PPI group in the future.

The most successfully recorded measure of compliance was the verbal report from participants. The majority reported they had taken all or ‘most’ of their vitamin D. Although the feasibility statement was 80% compliance with the vitamin D supplement, this statement is somewhat vague. It is not clear if this relates to 80% of patients taking their vitamin D or all patients taking 80% of their vitamin D supplements. It is not possible to derive a reliable percentage compliance from the collected data. Overall, 13/17 participants at 12 weeks, and 9/11 participants at 24 weeks reported taking all or ‘most’ of their vitamin D. Although ‘most’ is a subjective measure it does indicate that the majority of vitamin D supplements were taken. This suggests that taking the vitamin D supplement was broadly acceptable to participants. Raftery et al (2015) reported a 95% compliance with vitamin D supplementation in patients with CD. Although compliance is not clearly described in some vitamin D supplementation RCTs, many report that vitamin D supplementation is well tolerated (Jorgensen et al., 2010). Thus, the findings in the current study are consistent with other published vitamin D studies in IBD. A more definite but realistic statement of compliance will be required in a future trial. A pragmatic target would be 80% of participants taking ‘most’ of their vitamin D across the study period. The participant verbal report recommended by PPI appears to be a useful, although subjective, measure of this.

There are a number of studies reporting the use of periodic text messages to participants to improve compliance (Dale et al., 2015, Mayer and Fontelo, 2017). In a meta-analysis of 16 trials in chronic diseases the use of text messaging significantly improved medication adherence (OR, 2.11; 95% CI, 1.52-2.93; $p < .001$) (Thakkar et al., 2016). Therefore, this would be a useful strategy to include in a future study.

4.17.4 Compliance with study processes

It is essential to separate ‘missing’ data from data that was not collected or even requested from participants, such as during the first COVID-19 national lockdown, when assessing compliance. The feasibility target of completion of all trial processes in at least 80% of participants was rather unrealistic, particularly as the patient diaries were not expected to be successful. In addition, the impact of the COVID-19 pandemic means that this target was not achieved. Nevertheless, where requested, participants complied with nearly all study procedures.

The CDAI was calculated for all participants as requested. CDAI score suggested that most participants were in remission (<150) at each timepoint, with the number of patients with mild or moderate disease reducing by 24 weeks in both treatment arms. The CDAI tool uses height and weight data from participants to determine the standard deviation from normal weight as part of the overall CDAI score. These measurements may also be used to calculate Body Mass Index (BMI). However, BMI was not shown as a separate measurement or calculation within the study data analysis. In a future study, BMI calculation would be a useful addition to detect any correlation between level of malnutrition/obesity on vitamin D levels and symptoms.

All participants provided lifestyle data as requested for the final 28 week follow up appointment. All requested safety blood samples, iron studies, full blood count and CRP were collected with no issues during the study. Only one participant missed the collection of a hepcidin/vitamin D metabolite sample, which was due to an error in the sample collection process and not a problem with participant compliance. Although the results of the study demonstrate that it was feasible to collect and store samples for both hepcidin and vitamin D metabolites, the failure to process the

hepcidin samples was a disappointment. In addition, there were delays in the processing of the vitamin D metabolite samples at the University of Birmingham due to staffing issues. There was no formal contract in place for either of these blood tests and only funding allocated initially for the hepcidin samples. In a future study it would be necessary to ensure adequate funding is included for all samples to ensure staffing, and formal contracts in place to ensure completion of sample processing. Alternative laboratories would be approached for hepcidin analysis in any future study.

Nevertheless, the results from vitamin D metabolite analyses suggest some interesting correlations that are worth exploring in a larger, future study. Analysis of serum 25(OH)D3 is the most used measure of vitamin D status. Data in Figure 4-5 using a combination of all the patient data for multiple vitamin D metabolites showed that there was close correlation between serum 25(OH)D3 and values for 3epi-25(OH)D3 and 24,25$(OH)_2$D3. By contrast, although 25(OH)D2 levels were low in most patients, those individuals with slightly higher values for 25(OH)D2 also showed slightly lower serum 25(OH)D3. This suggests a reciprocal relationship between these two forms of vitamin D where higher levels of 25(OH)D2 might result in lower levels of 25(OH)D3 (Durrant et al., 2022). The precise reason for this is not clear but it was also interesting to note that serum 25(OH)D3 values less than 30 nmol/L were associated with a much high ratio of 25(OH)D3/24,25$(OH)_2$D3. This suggests that there is a threshold for induction of vitamin D catabolism but also underlines the fact that many of the CD patients were characterised by vitamin D deficiency. The use of vitamin D metabolite ratios has become more common in recent years as analytical technology has advanced. In a previous publication on the use of vitamin D

metabolite ratios, a ratio of 25(OH)D3/24,25$(OH)_2$D3 of between 10-15 was reported for 25(OH)D3 values between 20-200 nmol/L (Tang et al., 2019). This observation is consistent with the ratios observed for CD patients with serum 25(OH)D3 values higher than 30 nmol/L in the current study. However, serum 25(OH)D3 values less than 30 nmol/L were associated with much lower 25(OH)D3/24,25$(OH)_2$D3 ratios, suggesting that the 24-hydroxylation step is only weakly represented in these patients. This may be a mechanism for maximising the biological efficacy of very low serum 25(OH)D3 levels, without interference form catabolic pathways, but may also indicate that low serum 25(OH)D3 is simply associated with little or no biological response in these patients.

In terms of PROMs, all requested PROMs were completed and returned except one of the IBDQ/EQ5D5L booklets due at the 24 week follow up and one of the participant experience questionnaires at 28 weeks. These had been posted to the participants as per the protocol with a reply paid enveloped but were not received back despite a reminder being sent. The study was not powered to detect a statistical difference in PROM scores. Descriptively there was a slight downward trend in IBDQ/EQ5D5L scores suggesting a worsening quality of life, although this is difficult to interpret due to the amount of missing data and a small participant number. It is also important to recognise that CD patients in remission sometimes continue to report irritable bowel syndrome type symptoms, including abdominal pain and altered bowel habits (Szałwińska et al., 2021), with prevalence of symptoms as high as 29% of those in remission (Wang et al., 2021, Hoekman et al., 2017). This would be an important element to explore in IBDQ scores in a larger study.

Nonetheless, completion of PROMs as a paper-based booklet was successful in the current study. In a systematic review of 32 studies that included electronic PROMS, opposed to paper-based, response rates and data quality were improved, with participants finding the electronic modality acceptable (Meirte et al., 2020). However, electronic data capture may not be acceptable to all participants including those in older age groups (Hong et al., 2021). Therefore, in a future study it would be useful to consider both paper-based and electronic options for PROMS within PPI discussions.

The study processes that were least likely to be completed were the provision of a stool sample for faecal calprotectin and the completion of the patient diaries. In the results section missing stool samples are shown as protocol deviations. However, the protocol deviation table includes participants where a stool sample was not requested during the national lockdown and is therefore an over-estimate. Still, this is somewhat surprising, as a recent systematic review showed that clinical monitoring via stool sample analysis had a high acceptability rate among patients with IBD (Goodsall et al., 2020) and the PPI group did not identify provision of stool samples as an issue. This may be because stool samples are often routinely collected in clinical care and may become part of routine practice for patients. In the context of the study, it is possible that the timeframe in which the sample was required had an impact on recorded compliance. In the first versions of the protocol, stool samples had to be provided on the day of the clinic appointment, which may have been somewhat impractical for some participants. With the COVID-19 amendments there was more flexibility to provide samples within the study follow up window. However, participants would not be chased for samples outside of the protocol study follow up

windows, unlike clinical care. Strategies to improve compliance in this specific area would be the subject of future PPI discussions in any future study. In addition, the use of home testing kits for faecal calprotectin may be explored (Elkjaer et al., 2010, Hejl et al., 2018). Although a recent RCT showed that compliance was low (29%) with the home testing kit (Östlund et al., 2021), a patient experience study of 55 patients with IBD showed that over half found the kit easy to use (Wei et al., 2018). In this study 80% reported they would use it again in preference to providing samples for laboratory analysis. It will be important to ensure there is flexibility regarding provision of stool samples, so this may be a viable option for some patients.

4.17.5 Adverse events

Recording of AE's in trials is required by regulatory bodies but it is also clinically relevant in determining safety of treatments in patient groups (Friedman et al., 2010). Although patient numbers were small, with no serious AEs reported the results of the study suggest that the two vitamin D regimens were safe in the context of the current study. This is consistent with other vitamin D studies (Putzu et al., 2017, Mathur et al., 2017). In terms of the dose of vitamin D, a systematic review of studies giving doses of vitamin D <2800IU for prolonged periods of at least one year (15 RCTs, 3150 participants), found there was no increase in the risk of adverse events (Malihi et al., 2019). In the current study there were only three participants reporting causative AE's. Therefore, the feasibility target of absence of causative AE in 80% of participants was achieved.

4.17.6 Future Study

Most elements of the feasibility study were successful with good recruitment and motivated patient-participants. PPI input was effective with positive changes made to

the study design and methodology by the PPI group (Fletcher et al., 2021c). Ongoing PPI input would be crucial in the design of a future study.

The daily doses of vitamin D used were acceptable and well tolerated. However, the higher dose vitamin D 3,200IU was a specific brand that contained gelatine. Although only one patient declined to participate because they were vegan, in a future study it would be preferrable to identify vitamin D supplements that are acceptable to those observing a vegetarian or vegan diet, to ensure a wide representation of the population (Weikert et al., 2020).

As an open label study there was no blinding and participants were aware of their vitamin D supplement dose at randomisation. There is a clear need for blinding in placebo-controlled studies to reduce bias, however, in D-CODE all participants received a treatment. There is no evidence that participant's knowledge of their vitamin D dose affected any outcomes in the study. A study of hydration status in cyclists found no difference in outcomes between two groups of participants, with one group blinded and the other unblinded (Funnell et al., 2019). A recent meta-analysis of blinded and unblinded trials found no difference between reported treatment effects (Moustgaard et al., 2020). However, there is a risk that blinding might be lost during a trial (Webster et al., 2021) which may have skewed the results of the meta-analysis. Kahan et al., (2014) suggest that bias in unblinded trials may be mitigated by the use of objective measures. The use of a PROM as the primary outcome in D-CODE is a subjective measure. Nevertheless, it seems unlikely that knowing or not knowing their dose of vitamin D would affect a patient's response to questions such as "How often during the last 2 weeks have you been troubled by pain in the abdomen?". Blinding of IMP adds to study costs considerably. Although the open

label design of the feasibility study was a financially driven decision, it would be reasonable to use a pragmatic open label design again in a future RCT.

The COVID-19 management strategies, introduced later in the study, were clearly popular with participants and allowed them some flexibility. These strategies, such as the option of posting of vitamin D supplements and telephone follow up, would be included from the outset in any future study. This would not only be convenient for participants but would also allow rapid adaptation of the study in the event of future public health emergencies, such as a pandemic. Others have reported positive improvements to the management of trials due to changes made during the COVID-19 pandemic. These include the use of social media to recruit a more diverse, de-centralised patient group and the use of remote consent (Gaba and Bhatt, 2020), remote review/telemedicine and flexibility for participants in delivery of medication (Waterhouse et al., 2020). Exploration of the use of electronic PROMS and home testing kits for faecal calprotectin would further add to the accessibility of the study to a wide range of patients, who perhaps are not able to visit hospital regularly for study procedures.

Identification of participants for the feasibility study was via the concurrent vitamin D screening study. However, in a future RCT the vitamin D screening study may not run concurrently and so a different method of participant identification will be required. It is likely that two approaches will be included in a future protocol. Firstly, potential participants may be identified where vitamin D is measured within routine clinical care, and there is a 25(OH)D result <50nmol/L within the preceding couple of months. As in the current study vitamin D would be measured again following consent to participate to establish a current baseline. Alternatively, where there is no recent

25(OH)D result or where vitamin D is not measured for clinical reasons, patients may be consented to join a selection phase of the study to have vitamin D and other baseline biochemistry measured for the research. Where patients are found to have 25(OH)D >50nmol/L in the selection phase, they would be unable to proceed any further in the study.

Other key modifications required to the study protocol would include measuring compliance with the vitamin D supplement. The patient diaries were not well received, as expected. However, using patient reported compliance of all, most, some, or none of their supplements taken seems a workable and pragmatic solution in a low-risk trial and removes the burden of diaries. PTH was measured as a safety blood test to detect any participants who developed hyperparathyroidism during the study. However, the measurement of PTH seemed to add little useful safety information to the study. Patients with a known diagnosis of hyperparathyroidism or elevated calcium levels were already excluded (the exclusion criteria needed to be more specific and state this as primary hyperparathyroidism, although this is implicit). A recent study in 6280 patients reported only a 0.18% prevalence of primary hyperparathyroidism in people with normal calcium levels (Schini et al., 2020). For safety monitoring, calcium was measured at each follow up, so an abnormal calcium would have led to further clinical review without the need for routine monitoring of PTH in the study. Additionally, raised PTH levels may be seen in secondary hyperparathyroidism caused by vitamin D deficiency (Rejnmark et al., 2008). So, in this respect PTH was unhelpful and could be excluded in future.

4.17.7 Trial Management

The CTU had been commissioned by the Sponsor to carry out data management, statistical analysis, and study monitoring, including the development and provision of any required databases or systems to support this. However, to develop research skills further, JF undertook all trial management responsibilities within the study, in addition to all data collection. Reflection of the learning and development gained from this role is detailed in Appendix 11. In summary, JFs understanding of research processes and organisation was broadened. The opportunity allowed development of new skills to take forward into future studies, such as study and protocol design, understanding regulatory requirements and timescales and the role of CTUs.

Nevertheless, the trial manager role was intense and resulted in multiple competing elements which, as a lone-researcher, increased time pressure considerably. Apart from the extensive administrative aspects required within management of the study, there were numerous obligations to meet the requirements of the role from the CTU's perspective. As an honorary member of staff, JF was required to comply with all internal CTU processes including general training and attending team meetings. Although an excellent learning experience, in any future study the trial manager role would be most effectively carried out by a delegated person.

4.18 Limitations and Generalisability

The limitations of this study include the single-site opening in limiting the ability to assess this as a potential multi-site trial. The final number of participants consented and randomised is adequate for a feasibility study, despite the challenges placed on recruitment due to Sponsor temporarily halting the study. However, the lack of collected data from recruited participants during the initial phases of the COVID-19

pandemic, makes it difficult to interpret results. Nevertheless, there were no withdrawals from the study and the data that was collected suggests that participants were compliant with most trial processes. As a feasibility study the results are not generalisable. Instead, they indicate that it would be feasible to conduct D-CODE as a full RCT with modifications to the current protocol. Involvement of PPI would be crucial to address issues with some processes, such as the collection of stool samples, in a future study.

5 Thesis Conclusion

Within this thesis it has been established that patients with CD are at high risk of developing vitamin D deficiency, due to a variety of influencing factors. While this increases their risk of bone disease, there is also some observational evidence of non-skeletal effects. Vitamin D deficiency may have an adverse effect on CD related outcomes and health related quality of life. Despite this, monitoring for vitamin D deficiency in this patient group is not included in current national clinical guidelines. Indeed, guidance regarding the management of vitamin D deficiency in any patient group is diverse and conflicting.

The three studies conducted within this thesis followed a logical pathway in establishing the need for further robust research into vitamin D supplementation in patients with CD and vitamin D deficiency. The studies included a current practice survey, an observational vitamin D screening study and a feasibility study for a RCT of vitamin D supplementation in people with CD.

The current practice survey explored UK clinician's self-reported practice in the management of vitamin D deficiency in CD, and barriers to practice. A total of 62 members of the BSG, IBD section completed the web-based survey. Although the response rate was poor, the survey is the first published to date detailing clinician's self-reported practice and perceptions of barriers in this area of CD management. Results showed that survey participants were most likely to screen for vitamin D deficiency annually and in those patients who had had surgery related to their CD, despite the lack of clear national guidance directing them to do so. Consideration of several treatment options were reported, including vitamin D supplementation but also the use of sun exposure and diet modification in mild to moderate vitamin D

deficiency. Participants identified key barriers in practice; being a lack of evidence and a lack of clear national guidance. While the survey involved a small number of clinicians, the results highlight the need for further research to support the development of clinical guidelines.

The observational screening study estimated the prevalence of vitamin D deficiency among adults with CD in the local population. The study recruited 150 patients with CD during two separate recruitment periods (pre-COVID 19 pandemic and post COVID-19 pandemic national lockdown) and successfully utilised a DBS methodology as a minimally invasive procedure for measuring vitamin D serum levels. Results revealed that prevalence of vitamin D deficiency defined as 25(OH)D <50nmolL was 53.3%. This finding is consistent with other published Northern European studies (Caviezel et al., 2017, Frigstad et al., 2017). There was little difference in prevalence between the two recruitment periods.

Additionally, patient's modifiable risk factors for vitamin D deficiency, including intake of vitamin D containing foods, sun exposure and smoking were explored within the same study. Few patients were smokers, in keeping with clinical advice in the management of CD. A simple FFQ was used effectively to collect data on patients' usual weekly intake of five key vitamin D containing foods, as described by NHS England (2017). Overall patients within the study had a poor intake of vitamin D containing foods which is consistent with other studies that have explored dietary intake of vitamin D and vitamin D containing foods in patients with CD (Vagianos et al., 2007, Vagianos et al., 2016). In terms of sun exposure, the majority of patients reported that they tanned easily and would usually wear shorts and a short sleeved top if they were out in the sunshine. However, the use of high SPF was common, in

accordance with current public health advice on the prevention of skin cancer. These findings suggest that modification of diet and sun exposure in the treatment or prevention of vitamin D deficiency in this group is unlikely to be plausible. From this observational study in 150 patients, it can be suggested that the use of vitamin D supplementation should be considered as a mainstay of treatment and prevention of vitamin D deficiency in CD. However, the methodology utilised within this study, including DBS and the simplicity of question format, indicate that this study could be repeated remotely with a larger, multi-centre or dispersed population to provide more reliable evidence.

Determining the dose of vitamin D supplementation required to treat patients with malabsorptive disorders, such as CD, is challenging. One review suggested doses of vitamin D supplementation up to 10,000IU per day may be required in patients with IBD due to malabsorption (Hlavaty et al., 2015) but there is little supporting evidence for any specific dose in IBD or CD specifically. There are few RCTs exploring the use of vitamin D supplementation in IBD and results regarding non-skeletal benefits are conflicting, with a variety of vitamin D supplement doses trialled. The feasibility study for an RCT explored the use of two doses of vitamin D supplementation and PROMs to determine efficacy and non-skeletal benefits in patients with CD. In total 24 patients with 25(OH)D <50nmol/L were consented from the observational screening study. Of these, 22 patients were randomised to either Arm A 400IU vitamin D supplement daily for 24 weeks or Arm B 3,200IU daily for 12 weeks followed by 800IU vitamin D supplement daily for 12 weeks. There was a clear rationale for both dose regimens with Arm A being based on NICE (2017) guidance in at risk groups, and Arm B based

on the principle of a loading dose followed by a maintenance dose to treat vitamin D deficiency (Francis et al., 2018). All doses were licensed and commercially available.

The results of the feasibility study showed that, in this small cohort of patients, vitamin D levels increased in both study arms, but normal levels were achieved more rapidly in Arm B. The vitamin D supplements appeared to be safe and well tolerated in both study arms and there were no serious AEs reported. The first COVID-19 national lockdown impacted data collection. Nevertheless, most study processes were completed successfully by patients where requested, such as PROMs and blood tests. The study is feasible with some modifications. Indeed, the changes made to the protocol during the COVID-19 pandemic were positive improvements. Elements such as posting of IMP and PROMs and telephone follow up will be included in the design of the future RCT to make the study more accessible to a wider group of patients. This will be an important RCT for the future in establishing an evidence base for clinical practice.

In conclusion, the three studies comprising this thesis have demonstrated that patients in the UK with CD are at risk of vitamin D deficiency defined as 25(OH)D <50nmol/L. There is a clinical need for better evidence and clearer guidance in the detection and management of vitamin D deficiency in patients with CD, but that vitamin D supplementation is likely to be the mainstay of treatment. A RCT involving patients with identified vitamin D deficiency, using clinically relevant doses of vitamin D, is feasible to determine efficacy of treatments according to patient reported outcomes.

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7 Appendices

Appendix 1 Dissemination Plan

As results emerge at each stage of this study, they will be disseminated via publication and presentation at clinical and scientific conferences. In addition, the trial website www.dcode-trial.org.uk will be updated in a timely manner to ensure progress reports and results are easily accessible to a wide audience. Results will be disseminated regardless of the magnitude or direction of effect.

Key target audiences are nurses and medics working in gastroenterology areas. These practitioners are key in influencing changes in everyday practice in terms of screening for vitamin D deficiency in patients with CD. Publications will include findings from:

- Vitamin D screening study
- The feasibility clinical trial
- Patient and public involvement in the study

Publications

Publications will be in peer-reviewed journals. To maximise impact, journals that are most likely to be read by practitioners involved in the management of patients with CD will be selected in the first instance. In addition, specific results, such as the role of vitamin D and hepcidin monitoring in the feasibility trial, will be of interest to scientists and endocrinologists who specialise in the field of vitamin D research. For this reason, we will aim for publication in The Journal of Steroid Biochemistry and Molecular Biology.

As NIHR funded research, 28 days' notice will be given to the NIHR prior to any publication of results, where the NIHR will require an electronic copy of the accepted work. The NIHR will require an annual report detailing the progress and outputs generated from the research and the Clinical Doctoral Research Fellowship and an end of award report.

Presentations

Research results will be presented at national and international clinical and scientific meetings including.

- British Society of Gastroenterology Annual Meeting - This is an important venue for reaching a variety of practitioners involved in general gastroenterology care, including CD.
- The Vitamin D Workshop - this is an international scientific conference dedicated to stimulating research on vitamin D.
- The European Crohn's Colitis Organisation Congress is a pivotal venue in terms of influencing practice in the management of CD. Attendees will be from a variety of disciplines and European countries.
- Locally, results will be disseminated 6 monthly at departmental Gastroenterology meetings held at the recruiting centres.

Patient and public dissemination

- As per recommendations from the PPI group, strategies to disseminate information to the wider public will include social media/study website and patient groups such as Crohn's Colitis UK.

Appendix 2 – Current Practice Survey

Confidential

Vitamin D Screening in Crohn's Disease: Current Practice Survey

Thank you for taking a few moments to read this information.

You are invited to take part in a short survey regarding your current clinical practice in vitamin D screening in patients with Crohn's Disease. This research is funded by the National Institute for Health Research (NIHR) through a Clinical Doctoral Research Fellowship.

The survey should take about 5 minutes however you can save your answers and return to complete it at a later time. To avoid duplication of data it is important that you only complete the survey once.

The survey closes on 15th April 2019.

Thank you

Participant Information and Consent

Introduction
The purpose of this research project is to identify your current practice in monitoring for vitamin D deficiency in patients with Crohn's Disease and commonly recommended treatments for vitamin D deficiency. The research is being conducted by Jane Fletcher at University Hospitals Birmingham NHS Foundation Trust as part of a National Institute for Health Research (NIHR) Clinical Doctoral Research Fellowship.

Why have I received this?
You are invited to participate in this research project because you are a member of the British Society of Gastroenterology - IBD group. While there is no direct benefit to you in taking part it is hoped that your expert opinion and experience in the field may be used to influence future research and treatments for patients with Crohn's Disease.

What does it involve?
The research involves completing an online survey that will take approximately 5-10 minutes. Your responses will be treated confidentially. The survey questions will be about your usual clinical practice in measuring vitamin D levels in patients with Crohn's Disease and treatment of vitamin D deficiency in this patient group. It is important that you complete the survey only once to avoid duplication of data.

Your participation in the survey is voluntary and you may choose to withdraw at anytime. The data you have provided prior to withdrawal will be used to inform the overall results of the survey. You will not be able to withdraw data once submitted. All data is stored in a password protected electronic format. The results of this study will be presented at professional conferences and meetings and published in relevant medical journals.

Confidentiality
We are not collecting any identifiable information during the survey.

Ethical approval
This research has received ethical approval from the University of Birmingham

Contact
If you have any queries regarding the survey please contact Jane Fletcher, Nutrition Nurse Lead, Queen Elizabeth Hospital Birmingham:
Telephone: 0121 371 4561 Email: jane.fletcher@uhb.nhs.uk.

Funding
This publication presents independent research funded by the National Institute for Health Research (NIHR) and Health Education England through a Clinical Doctoral Research Fellowship, Jane Fletcher ICA-CDRF-2017-03-083. The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care

☐ I agree to participate in the survey

○ I do not wish to participate in the survey

Vitamin D Screening

The following questions are about your usual practice in checking vitamin D levels for patients with Crohn's Disease.

1 Do you think vitamin D levels should be routinely checked in patients with Crohn's Disease? (select one)

- ○ Yes
- ○ No

1a Why do you think this? (select all that apply)

- ☐ Lack of guidance
- ☐ Lack of evidence
- ☐ Too expensive
- ☐ Not in my Trust guidelines/protocol
- ☐ Not necessary in this patient group
- ☐ Other

1b If 'Other', please specifiy

_____

2 Approximately how often do you check vitamin D levels in patients with the following types of Crohn's Disease? (select one for each)

	3 monthly	6 monthly	Annually	Rarely or never
Small Bowel Crohn's Disease	○	○	○	○
Crohn's Colitis	○	○	○	○
Perianal Crohn's Disease	○	○	○	○

3 Approximately how often do you check vitamin D levels in patients with Crohn's Disease receiving the following treatment? (select one for each treatment)

	3 monthly	6 monthly	Annually	Rarely or never
Immuno-modulators	○	○	○	○
Biologic Therapy	○	○	○	○
Steroids	○	○	○	○
History of previous surgery due to Crohn's Disease	○	○	○	○

4 Are you aware of any guidelines related to monitoring vitamin D in patients with Crohn's Disease? (select all that apply)

- ☐ Local or Trust
- ☐ Regional
- ☐ National
- ☐ European
- ☐ Worldwide
- ☐ Not aware of any

4a Please specify any guidelines that you are aware of

_____

5 Does the season determine whether you are more likely to check vitamin D levels in a patient with Crohn's Disease?

- ◯ Yes
- ◯ No

6 Does the patient's ethnicity determine whether you are more likely to check vitamin D levels in patients with Crohn's Disease?

- ◯ Yes
- ◯ No

6a Please give more detail for your answer:

_____

7 Are there any other cultural, religious or socio-economic factors that would influence your decision to check vitamin D levels in a patient with Crohn's Disease?

- ◯ Yes
- ◯ No

7a Please give more detail for your answer

_____

8 If you do not routinely monitor vitamin D levels in patients with Crohn's Disease what is most likely to influence your practice? (select all that apply)

- ☐ Clear guidance
- ☐ Better clinical evidence
- ☐ Stipulated in my Trust protocol/guidelines
- ☐ Relevant education
- ☐ Patient request
- ☐ National media
- ☐ I would not change my current practice
- ☐ Not applicable, I already monitor vitamin D levels

The following question is about your usual practice in recommending treatment for vitamin D deficiency.

At what level would you recommend the following as a treatment for vitamin D deficiency in patients with Crohn's Disease? (This might be different for different types of Crohn's Disease but consider Crohn's patients you see most commonly in your clinical practice)

	Mild deficiency (35-49 nmol/l)	Moderate deficiency (15 - 34 nmol/l)	Severe deficiency (< 15nmol/l)
Increase sunlight exposure	☐	☐	☐
Dietary advice to increase vitamin D derived from foods	☐	☐	☐
Oral vitamin D supplementation	☐	☐	☐
Intramuscular vitamin D supplementation	☐	☐	☐
I would not recommend treatment	☐	☐	☐

9a Please give more detail for your answer

The following questions are about any other types of nutritional monitoring you may carry out and investigations in to bone disease in patients with Crohn's Disease.

10 Do you routinely measure any of the following in patients with Crohn's Disease? (select all that apply)

- ☐ Body mass index (BMI)
- ☐ Fat soluble vitamins A and E
- ☐ Iron Studies including ferritin
- ☐ Folate
- ☐ Vitamin B12
- ☐ Zinc
- ☐ Copper
- ☐ Selenium
- ☐ Magnesium
- ☐ I don't check any of these

11 What would be a trigger for you to carry out investigations in to bone health, such as DEXA scan, in a patient with Crohn's Disease? (select all that apply)

- ☐ Vitamin D deficiency
- ☐ Duration of Crohn's Disease
- ☐ Severity of Crohn's Disease
- ☐ Presence of malnutrition
- ☐ Recurrent steroid use
- ☐ Guideline recommendation
- ☐ Other
- ☐ I would not investigate bone health

11a Please specify _____

12 Any other comments you would like to make?

The final section is about you.

13 What is your professional group? (select one from the dropdown box)

- ◯ Gastroenterology Consultant
- ◯ Gastroenterology Resigtrar
- ◯ Pathologist
- ◯ Radiologist
- ◯ Surgeon
- ◯ Registered Nurse
- ◯ Allied Health Professional

14 What is your age group?

- ◯ 20-29 years
- ◯ 30-39 years
- ◯ 40-49 years
- ◯ 50-59 years
- ◯ 60-69 years
- ◯ 70+ years

15 What geographical area is your usual place of work in the UK?

◯ Scotland ◯ North East England ◯ North West England ◯ Midlands (England) ◯ Wales ◯ London ◯ South East England ◯ South West England ◯ Northern Ireland ◯ I am based outside of the UK

16 In what setting is your usual place of work?

☐ University teaching hospital ☐ District General Hospital ☐ Primary Care ☐ University academic

Appendix 3 Data Management Plan – Current Practice Survey

Project Title
Current Practice Survey: vitamin D deficiency in patients with Crohn's Disease - screening and treatment
1. Description of the data
1.1 Type of study The study is a web-based survey involving healthcare professionals who care for patients with Crohn's Disease across the UK. **1.2Types of data** Quantitative and qualitative data will be collected using the web-based survey designed on REDCap. **1.3Format and scale of the data** Data will be exported by the CI from REDCap to IBM SPSS software for analysis of data and production of graphs.
2. Data collection/generation
2.1 Methodologies for data collection / generation Study data will be collected anonymously and managed using REDCap electronic data capture tools hosted at University of Birmingham **2.2 Data quality and standards** Data will be collected in accordance with the requirements of the Data Protection Act 2018 and GDPR 2018. No personal or identifiable data will be collected by the study team. Non-identifiable demographic data will be collected to inform the results of the survey. During the pilot study a link to the survey will be emailed to known members of the UHB gastroenterology team via UHB email addresses. However, return of data will be anonymous. During the main study, the study team will not have access to any personal contact details such as email addresses. The survey link and information will be sent to a named individual within the BSG with approved and legitimate access to membership lists, who will send the survey link to members on behalf of the study team.
3. Data management, documentation and curation
3.1 Managing, storing and curating data. The final study dataset will be protected by restricted, login access to REDCap and the specific project area. Access will be available only to the CI and the study supervisory team at the University of Birmingham and clinical supervisor at University Hospitals Birmingham.

3.3 Data preservation strategy and standards

At the end of the study research data will be stored for 10 years as per University of Birmingham research records retention policy. Data will be stored in the Birmingham Environment for Academic Research (BEAR) Research Data Archive. This is a secure, backed up data storage service hosted by the University of Birmingham.

Data Sharing

Data will be stored in the University of Birmingham UBIRA eData Repository for 10 years as per the University of Birmingham Data Management Policy.

4. Data confidentiality

N/A Study data will be collected anonymously

5. Data sharing and access

5.1 Discovery by potential users of the research data

Data will be published in appropriate high impact open access peer reviewed journals to target appropriate academic audiences. Data will be presented and accessible in published open access abstracts at national and international conferences. Through existing collaborations data will be available to researchers at the University of Birmingham and other UK Universities, as well as selected groups in the USA.

5.2 Governance of access

The PI will govern access to data, prior to and following publication. The PI and College of MDS are fully committed to sharing data in an appropriate manner, and all requests for access to data will be welcome

5.3 PI group exclusive use of data

Prior to publication, limited data will be shared at national and international conferences. Upon publication, all affiliated data covered in the paper and modified organisms will be freely available on request.

5.4 Restrictions or delays to sharing, with planned actions to limit such restrictions
In instances where intellectual property arising from the research is identified, there may be delays in sharing data to ensure this is sufficiently protected. Where appropriate, data protection will be established prior to publication to prevent this.

6. Responsibilities

The PI will be responsible for implementing the plan. However, individual researchers will be responsible for metadata creation, quality assurance and data security.

7. Institutional, departmental or study policies

Policy	Reference
Data Management Policy & Procedures; Data Security Policy; Data Sharing Policy; Institutional Information Policy	Data Protection Act 1998 GDPR 2018
8. Author of Data Management Plan	
Jane Fletcher 27022019	

Appendix 4 Regulatory Approvals for D-CODE

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Mrs Jane Fletcher
Queen Elizabeth Hospital Birmingham
4-59 4th Floor, East Block
Edgbaston, Birmingham
B15 2TH

Email: hra.approval@nhs.net
Research-permissions@wales.nhs.uk

12 March 2019

Dear Mrs Fletcher

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Can Vitamin D Supplementation in Patients with Crohn's Disease Improve Symptoms as an Adjunct Therapy: D-CODE Feasibility Study**
IRAS project ID:	**255005**
EudraCT number:	**2018-003910-42**
Protocol number:	**RRK6542**
REC reference:	**19/NE/0019**
Sponsor	**University Hospitals Birmingham NHS Foundation Trust**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

How should I continue to work with participating NHS organisations in England and Wales?
You should now provide a copy of this letter to all participating NHS organisations in England and Wales, as well as any documentation that has been updated as a result of the assessment.

This is a single site study sponsored by the site. The sponsor R&D office will confirm to you when the study can start following issue of HRA and HCRW Approval.

It is important that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details of the research management function for each organisation can be accessed here.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?

HRA and HCRW Approval does not apply to NHS/HSC organisations within the devolved administrations of Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) has been sent to the coordinating centre of each participating nation. You should work with the relevant national coordinating functions to ensure any nation specific checks are complete, and with each site so that they are able to give management permission for the study to begin.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?
The document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

I am a participating NHS organisation in England or Wales. What should I do once I receive this letter?
You should work with the applicant and sponsor to complete any outstanding arrangements so you are able to confirm capacity and capability in line with the information provided in this letter.

The sponsor contact for this application is as follows:

Name: Dr Christopher Counsell
Tel: 01213714184
Email: chris.counsell@uhb.nhs.uk

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **255005**. Please quote this on all correspondence.

Yours sincerely

Helen Penistone
Assessor

IRAS project ID	255005

Tel: 0207 104 8010
Email: hra.approval@nhs.net

Copy to: *Dr Christopher Counsell, University Hospitals Birmingham NHS Foundation Trust (Sponsor and lead NHS R&D contact)*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
MHRA CTA		08 January 2019
Copies of advertisement materials for research participants [DCODE Poster]	1.0	30 November 2018
Covering letter on headed paper [Ethics cover letter]	1.0	17 December 2018
GP/consultant information sheets or letters [GP letter - winter screening]	1.0	16 November 2018
GP/consultant information sheets or letters [GP letter - vitamin D result]	1.0	16 November 2018
GP/consultant information sheets or letters [GP letter - feasibility recruitment]	1.0	18 November 2018
GP/consultant information sheets or letters [GP letter - perceived benefit]	1.0	16 November 2018
GP/consultant information sheets or letters [GP letter - summer screening]	1.0	16 November 2018
IRAS Application Form [IRAS_Form_27122018]		27 December 2018
Letter from funder		
Letter from funder [NIHR Letter of Intent]		26 February 2018
Non-validated questionnaire [IBDQ (non stoma)]	2.0	14 December 2018
Non-validated questionnaire [IBDQ (stoma)]	2.0	14 December 2018
Non-validated questionnaire [End of trial patient experience]	2.0	14 December 2018
Other [Response Letter to REC - Conditions]	2	01 March 2019
Other [confirmation from MHRA that study is a CTIMP]		04 April 2016
Other [Summary of Product Characteristics Fultium D3 800iu]		09 January 2018
Other [Safety Data Sheet Fultium Daily 400iu]		25 April 2017
Other [Thank you letter screening study]	1.0	18 November 2018
Other [Thank you letter supplementation study]	1.0	18 November 2018
Participant information sheet (PIS) [PIS 1 - Winter Screening]	2	28 February 2019
Participant information sheet (PIS) [PIS 2 - Vitamin D Supplementation]	2	28 February 2019
Participant information sheet (PIS) [PIS 3 - Summer Screening]	2	28 February 2019
Referee's report or other scientific critique report [NIHR Panel Review Summary]	1.0	18 May 2017
Research protocol or project proposal [DCODE protocol]	1.0	03 December 2018
Sample diary card/patient card [Patient Diary]	1.0	03 December 2018
Summary CV for Chief Investigator (CI) [Jane Fletcher CV]		
Summary CV for supervisor (student research) [D Carrick Sen CV]		
Summary CV for supervisor (student research) [M Hewison CV]		
Summary of product characteristics (SmPC) [Fultium D3 3,200iu]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Patient Pathway]	1.0	30 November 2018

Summary of assessment

The following information provides assurance to you, the sponsor and the NHS in England and Wales that the study, as assessed for HRA and HCRW Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England and Wales to assist in assessing, arranging and confirming capacity and capability.

Assessment criteria

Section	Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	The sites named on the IRAS form have now merged in to one Trust and are now all University Hospitals Birmingham NHS Trust.
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a single site study taking place in the NHS where the site is also sponsoring the study. Therefore, no agreement is expected.
4.2	Insurance/indemnity arrangements assessed	Yes	No comments
4.3	Financial arrangements assessed	Yes	Funding has been granted by the NIHR.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Yes	No comments
5.3	Compliance with any applicable laws or regulations	Yes	No comments

NHS
Health Research Authority
North East - Newcastle & North Tyneside 2 Research Ethics Committee

NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Tel: 0207 104 8082

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

06 February 2019

Mrs Jane Fletcher
Queen Elizabeth Hospital Birmingham
4-59 4th Floor, East Block
Edgbaston, Birmingham
B15 2TH

Dear Mrs Fletcher

Study title:	**Can Vitamin D Supplementation in Patients with Crohn's Disease Improve Symptoms as an Adjunct Therapy: D-CODE Feasibility Study**
REC reference:	**19/NE/0019**
Protocol number:	**RRK6542**
EudraCT number:	**2018-003910-42**
IRAS project ID:	**255005**

The Research Ethics Committee reviewed the above application at the meeting held on 23 January 2019. Thank you for attending to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below. .

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

1) Amend study documentation to exclude pregnant women.

2) The Participant Information Sheet was to be amended with the following:
   a) Include a sentence to explain that patient's GPs would be informed of their participation in the study and if patients did not consent to this they would be excluded.
   b) Include a sentence to state that the study information would be sent out with the appointment letter.

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites listed in the application taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites

The Committee has not yet completed any site-specific assessment(s) (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Extract of the meeting minutes

Mrs Fletcher and Professor Hewison were welcomed by the Chair and joined the meeting for discussion.

The Chair informed Mrs Fletcher and Professor Hewison that there were observers in attendance at the meeting and that they could request that the observers be asked to leave if they wished to do so. They confirmed that they had no objection to the observers being present.

Social or scientific value; scientific design and conduct of the study

Members noted that this was a meaningful, worthwhile and interesting pilot study and congratulated the applicant on the level of Patient and Public Involvement.

Mrs Fletcher thanked the Committee for their comments.

Members queried whether a pregnancy test was required.

Mrs Fletcher replied that this was only an intervention study and were not carrying out screening.

The Committee was satisfied with the response given to the issue raised.

Informed consent process and the adequacy and completeness of participant information

Members queried whether patients would have enough time to consent.

Mrs Fletcher replied that participants could undertake the screening test on the same day as their appointment however this could additionally be undertaken at a follow-up appointment to allow further time to consider.

Members asked whether the poster was created for the purpose of recruitment.

Mrs Fletcher replied that the poster was to inform people about the study and not for recruitment purposes.

The Committee was satisfied with the responses given to the issues raised above.

Members queried whether GPs would be informed.

Mrs Fletcher replied that there was a template letter that would be sent to the GP if they participated but would only be sent with the patients consent. A note would be included in their medical records.

Members were in agreement that the participants' GP needed to be informed and those patients, who did not consent to this, should therefore be excluded from participating in the study.

The applicants accepted this point and would amend the documentation accordingly.

Members queried whether the Participant Information Sheet could be sent out with the appointment letter.

Mrs Fletcher replied that the leaflet could be sent out with the appointment letter and would ensure that the documentation was amended.

Members stated that the information sheets under section "Will my participation be kept confidential?" on page 3, "When you agree to take part in a research study, the information... and in other organisations." was very broad and related to sharing of data with others.

Mrs Fletcher replied that the patients' details would not be shared and this had come from the Clinical Trials Unit.

The Committee asked that these two paragraphs be removed from the document.

The applicants accepted this point.

Mrs Fletcher and Professor Hewison left the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [DCODE Poster]	1.0	30 November 2018
Covering letter on headed paper [Ethics cover letter]	1.0	17 December 2018
GP/consultant information sheets or letters [GP letter - winter screening]	1.0	16 November 2018
GP/consultant information sheets or letters [GP letter - vitamin D result]	1.0	16 November 2018
GP/consultant information sheets or letters [GP letter - feasibility recruitment]	1.0	18 November 2018
GP/consultant information sheets or letters [GP letter - perceived benefit]	1.0	16 November 2018
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Non-validated questionnaire [End of trial patient experience]	2.0	14 December 2018
Non-validated questionnaire [IBDQ (non stoma)]	2.0	14 December 2018
Non-validated questionnaire [IBDQ (stoma)]	2.0	14 December 2018
Other [Summary of Product Characteristics Fultium D3 800iu]		09 January 2018
Other [Safety Data Sheet Fultium Daily 400iu]		25 April 2017
Other [Thank you letter screening study]	1.0	18 November 2018
Other [Thank you letter supplementation study]	1.0	18 November 2018
Other [confirmation from MHRA that study is a CTIMP]		04 April 2016
Participant information sheet (PIS) [Participant information and consent 1]	1.0	13 December 2018
Participant information sheet (PIS) [Participant information and consent 2]	1.0	13 December 2018
Participant information sheet (PIS) [Participant information and consent 3]	1.0	13 December 2018
Referee's report or other scientific critique report [NIHR Panel Review Summary]	1.0	18 May 2017
Research protocol or project proposal [DCODE protocol]	1.0	03 December 2018
Sample diary card/patient card [Patient Diary]	1.0	03 December 2018
Summary CV for Chief Investigator (CI) [Jane Fletcher CV]		
Summary CV for supervisor (student research) [D Carrick Sen CV]		
Summary CV for supervisor (student research) [M Hewison CV]		
Summary of product characteristics (SmPC) [Fultium D3 3,200iu]		
Summary, synopsis or diagram (flowchart) of protocol in non	1.0	30 November 2018

technical language [Patient Pathway]		

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

19/NE/0019	Please quote this number on all correspondence

With the Committee's best wishes for the success of this project.

Yours sincerely

pp

Professor Andrew Hall
Chair

E-mail: nrescommittee.northeast-newcastleandnorthtyneside2@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers"

Copy to: *Dr Christopher Counsell, University Hospitals Birmingham NHS Foundation Trust*

North East - Newcastle & North Tyneside 2 Research Ethics Committee

Attendance at Committee meeting on 23 January 2019

Committee Members:

Name	*Profession*	*Present*	*Notes*	
Mrs Ann Boardman	Retired Educationalist	Yes		
Mr Andrew Brenikov	Historian	Yes		
Dr Raymond Chadwick	Postgraduate Tutor in Clinical Psychology	Yes		
Professor Andrew Hall (Chair)	Former Associate Dean for Bio Resources	Yes		
Miss Phillipa Hearty	Research Assistant	Yes		
Dr Tony Newton	Director	Yes		
Mrs Susan P Phillips	Clinical Lead Pharmacist	Yes		
Dr Meiyi Pu	Consultant	Yes		
Mr Thomas Smith	Lay Member	Yes		
Ms Emma Thompson	Research Radiographer	Yes		
Mrs Susan Webster	Head of Psychology	No		

Also in attendance:

Name	*Position (or reason for attending)*	
Miss Kerry Dunbar	REC Manager	

NHS
Health Research Authority
North East - Newcastle & North Tyneside 2 Research Ethics Committee

NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Tel: 0207 104 8082

Please note: This is an acknowledgement letter from the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

08 March 2019

Mrs Jane Fletcher
Queen Elizabeth Hospital Birmingham
4-59 4th Floor, East Block
Edgbaston, Birmingham
B15 2TH

Dear Mrs Fletcher

Study title:	**Can Vitamin D Supplementation in Patients with Crohn's Disease Improve Symptoms as an Adjunct Therapy: D-CODE Feasibility Study**
REC reference:	**19/NE/0019**
Protocol number:	**RRK6542**
EudraCT number:	**2018-003910-42**
IRAS project ID:	**255005**

Thank you for your letter of 01 March 2019. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 06 February 2019

Documents received

The documents received were as follows:

Document	*Version*	*Date*
Other [Response Letter to REC - Conditions]	2	01 March 2019
Participant information sheet (PIS) [PIS 3 - Summer Screening]	2	28 February 2019
Participant information sheet (PIS) [PIS 1 - Winter Screening]		28 February 2019
Participant information sheet (PIS) [PIS 2 - Vitamin D Supplementation]	2	28 February 2019
Response to Additional Conditions Met		05 March 2019

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	*Version*	*Date*
Copies of advertisement materials for research participants [DCODE Poster]	1.0	30 November 2018
Covering letter on headed paper [Ethics cover letter]	1.0	17 December 2018
GP/consultant information sheets or letters [GP letter - winter screening]	1.0	16 November 2018
GP/consultant information sheets or letters [GP letter - vitamin D result]	1.0	16 November 2018
GP/consultant information sheets or letters [GP letter - feasibility recruitment]	1.0	18 November 2018
GP/consultant information sheets or letters [GP letter - perceived benefit]	1.0	16 November 2018
GP/consultant information sheets or letters [GP letter - summer screening]	1.0	16 November 2018
IRAS Application Form [IRAS_Form_27122018]		27 December 2018
IRAS Checklist XML [Checklist_27122018]		27 December 2018
Letter from funder [NIHR Letter of Intent]		26 February 2018
Non-validated questionnaire [End of trial patient experience]	2.0	14 December 2018
Non-validated questionnaire [IBDQ (non stoma)]	2.0	14 December 2018
Non-validated questionnaire [IBDQ (stoma)]	2.0	14 December 2018
Other [Summary of Product Characteristics Fultium D3 800iu]		09 January 2018
Other [Safety Data Sheet Fultium Daily 400iu]		25 April 2017
Other [Thank you letter screening study]	1.0	18 November 2018
Other [Thank you letter supplementation study]	1.0	18 November 2018
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Participant information sheet (PIS) [PIS 1 - Winter Screening]	2	28 February 2019
Participant information sheet (PIS) [PIS 2 - Vitamin D Supplementation]	2	28 February 2019
Participant information sheet (PIS) [PIS 3 - Summer Screening]	2	28 February 2019

Referee's report or other scientific critique report [NIHR Panel Review Summary]	1.0	18 May 2017
Research protocol or project proposal [DCODE protocol]	1.0	03 December 2018
Response to Additional Conditions Met		05 March 2019
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Summary CV for supervisor (student research) [D Carrick Sen CV]		
Summary CV for supervisor (student research) [M Hewison CV]		
Summary of product characteristics (SmPC) [Fultium D3 3,200iu]		
Summary, synopsis or diagram (flowchart) of protocol in non technical language [Patient Pathway]	1.0	30 November 2018

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

19/NE/0019 **Please quote this number on all correspondence**

Yours sincerely

Kerry Dunbar
REC Manager

E-mail: nrescommittee.northeast-newcastleandnorthtyneside2@nhs.net

Copy to: *Dr Christopher Counsell, University Hospitals Birmingham NHS Foundation Trust*

Medicines & Healthcare products Regulatory Agency

MHRA

MHRA
10 South Colonnade
Canary Wharf
London
E14 4PU
United Kingdom

gov.uk/mhra

Ms J Fletcher
UNIVERSITY HOSPITALS BIRMINGHAM NHS FOUNDATION TRUST
4-59, 4TH FLOOR EAST BLOCK, QUEEN ELIZABETH HOSPITAL
MINDELSOHN WAY, EDGBASTON
BIRMINGHAM
B15 2TH
UNITED KINGDOM

08/01/2019

Dear Ms J Fletcher

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031 (as amended)(the 'Regulations')

Our Reference:	16719/0234/001-0001
Eudract Number:	2018-003910-42
Product:	Fultium Daily D3 Capsules
Protocol number:	RRK6542

ACKNOWLEDGEMENT OF NOTIFICATION

I am writing to confirm receipt of your notification of a clinical trial received on 17/12/2018.

For the purposes of regulation 18(2)(c) or 20(2)(a) and (5) of the Regulations (as appropriate), this letter is notice of authorisation of the trial referenced above with effect from 31/12/2018 (the 'effective date') subject to the following condition:

- that no further correspondence is received from the Licensing Authority before the effective date requiring full assessment of your request for authorisation.

You are reminded that your trial may be suspended or terminated at any time by the Licensing Authority in accordance with regulation 31. You must notify the Licensing Authority within 90 days of the trial ending.

Finally, you are reminded that a favourable opinion from the Ethics Committee is also required before this trial can proceed.

Yours sincerely,

Medicines & Healthcare products
Regulatory Agency

MHRA

Clinical Trials Unit
MHRA

Appendix 5 D-CODE Poster Designed by the PPI Group

Appendix 6 Chronology of D-CODE Protocol Amendments

Version 6 19/01/2022

Amendment	Rationale	Page number (s)
Hepcidin blood samples removed from the protocol	Specialist analysis of these samples is no longer available in the UK	19,29,39,31,40,44, 45,48,49,79

Version 5.0 13/10/2020

Primary reason for the amendment was the introduction of COVID-19 management strategies to protect participants and the public as per HRA and MHRA guidance.

Amendment	Rationale	Page number (s)
Patients' appointments will be via face to face, telephone, or video consultation according to their needs	To reduce the risk of face-to-face contact due to the COVID-19 pandemic	32, 34, 37, 63

Patients attending for their routine CD follow up or infusion unit out-patient appointment will be identified by their Gastroenterologist for inclusion in the screening study.	Few patients are attending outpatient clinics due to the COVID-19 pandemic, but continue to attend infusion units for treatment	33
Patient reported outcome measures will be posted to participants as appropriate with their consent, along with a reply-paid return envelope.	To reduce the risk of face-to-face contact due to the COVID-19 pandemic	34, 41
Trial medication may be posted to participants with their consent via a tracked service. Participants will be provided a reply-paid envelope to return any unused IMP they have remaining at the end of the study,	To reduce the risk of face-to-face contact due to the COVID-19 pandemic	36, 46
Where participants are not able to attend the hospital for blood tests these may be arranged at a Trust off-	To reduce hospital attendances due to the COVID-19 pandemic	39, 63

site phlebotomy centre. Hepcidin and vitamin D metabolites will not be collected at an off-site centre. Where participants are self-isolating or are not able to attend for blood tests within the follow up window, trial medication will be provided following assessment by the PI and blood tests arranged at the earliest opportunity when the participant is able to attend or no longer isolated. Where participants are self-isolating and are not able to attend for blood tests or delivery of samples, these may be carried out at the participant's home address with their verbal consent and according to the Trust lone-worker procedure.	To reduce the risk of face-to-face contact due to the COVID-19 pandemic To reduce hospital attendances due to the COVID-19 pandemic	

Participant visits changed to appointments	Appointments may be via video or telephone to reduce hospital face to face visits	37, 49
The PI is responsible for ensuring all SAEs forms are emailed immediately to the CTU Central Safety Team (CST) LCTCsafe@liverpool.ac.uk unless the SAE is specified in the protocol as not requiring immediate reporting.	Change in SAE reporting process at the CTU from faxing of SAE forms to direct email to lctcsafe@liverpool.ac.uk	61, 62

Version 4.0 04/3/2020

Following the serious breach: Primary reason for the amendment were changes to make elements of the research easier for participants and to strengthen the wording around randomisation and PROMS.

Amendment	**Rationale**	**Page number (s)**
Change of CI and co-investigator	CI is an experienced PI who has previous experience of a CTIMP	2, 8

Final follow up at 28 weeks	This is adequate time to allow effective follow up of participants while reducing time burden of study duration	14, 33, 37
Final follow up at 28 weeks will be via telephone consultation and postal questionnaire	Reduce the time burden for participants. No invasive procedures are required for this follow up.	14, 33, 37,
Addition of posting of a copy of the signed consent form to participants	Ensure participants receive a copy of their signed consent form	28
Removed specific time periods for participant to consider study information prior to consent	Ensure participants have adequate time to consider information within the recruitment period	29, 30
Removal of a specific time period for posting of the G.P. letter	Allow adequate time for return of results to site prior to informing G.P.	30
Clarification of the process for medical confirmation of eligibility prior to participants attending for a further appointment.	Reduce the burden for participants in attending an appointment before they are deemed eligible	31

Clarification that a faecal calprotectin collected within the last month from the clinical team will be used for the purposes of the study	To reduce the burden to participants of providing multiple stool samples.	31
Removal of the washout period	A washout period for vitamin D is not clinically indicated in the study	31
Clarification that questionnaires are completed prior to the patient being given the IMP	Ensure clarity over study procedures	31
Removal of the requirement of the patient specifically to present the prescription at pharmacy	Ensure prescription is presented where the patient is not able to access the clinical trials pharmacy	32

Version 3.0 12/12/2019

Primary reason for the amendment was because Fultium daily 400iu was discontinued by the manufacturer. Need to change terminology in the protocol to generic vitamin D3.

Amendment	**Rationale**	**Page number (s)**

CTRC changed to LCTC	The Liverpool Cancer Trials Unit (LCTU) and the Clinical Trial Research Centre (CTRC) have merged to become the Liverpool Clinical Trials Centre (LCTC).	3, 11
Sponsor contact name updated	Ensure current contact details are contained within the protocol	5
Removed specific brand of Vitamin D3 and changed to the drug generic name of Cholecalciferol	To allow use of an appropriate vitamin D3 supplement rather than a specific brand	13, 18,19,21,39,40, 41,42, 48
Updated IMP 400IU marketing authorisation information	As per summary of product characteristics	40
Updated IMP 400IU reference safety information	As per summary of product characteristics	48
Removed information related to specific University Hospital Birmingham NHS Trust hospital laboratories.	Hospital laboratories are part of the same NHS Trust. More detailed information regarding	34

	analysis of samples is contained within the laboratory manual	

Version 2.0 10/05/2019

Primary reason for the amendment was to remove reference to specific seasons as the study had not started on time and the seasonal element was no longer possible.

Amendment	**Rationale**	**Page number (s)**
Updated LCTC address and contact details	Ensure correct information available	4
Removal of reference to specific seasons (winter or summer)	The study has not started according to schedule. Therefore, the planned specific seasonal elements are no longer possible due to time restrictions.	10,12,19,20,21, 23,26,27,30, 51
Denote that faecal calprotectin will be measured twice at 0 and 24 weeks	Faecal calprotectin reduced to twice from three times due to financial restrictions	13, 31

Correction of minor errors including depicting months in weeks, spelling mistakes	Ensure accuracy and clarity	16,17, 36, 38
Deleted season specific vitamin D screening participant information sheet. One generic information sheet for the vitamin screening studies.	The study has not started according to schedule. Therefore, the planned specific seasonal elements are no longer possible due to time restrictions.	25
Additional information regarding posting participant information sheets to patients prior to their outpatient appointment	In accordance with Research Ethics Committee Recommendations	26
Deleted reference to sample logs	Sample logs are not required as normal NHS Laboratory processes are being followed.	33, 34
Amended SPC to safety data sheet for Fultium Daily	Ensure the correct safety information is referenced.	39

Addition of a pragmatic verbal report of IMP compliance by participants	Recommended by the Trial Steering Committee that a verbal report should be used in addition to diaries to measure participant compliance.	40
Addition of information related to recording concomitant medication.	Medication started or stopped within 2 weeks prior to randomisation will be recorded to ascertain recent vitamin D supplementation use.	41

Appendix 7 Vitamin D Screening Study Participant Information Sheet

University Hospitals Birmingham NHS Trust
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
Birmingham B15 2GW
Telephone: 0121 627 2000

D-CODE Feasibility Study

Vitamin D Screening in People with Crohn's Disease

You are invited to take part in D-CODE

- In this study, we will be screening about 250 people with Crohn's Disease to check if they have vitamin D deficiency.
- If you wish to take part we will ask you to sign a consent form giving us permission to take a finger-prick blood sample from you to check your vitamin D level and to use the information you give us for research.
- Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully and discuss it with friends or relatives if you wish.
- Taking part is voluntary. If you don't want to take part then you don't need to give a reason.
- Please ask a member of your clinical team if there is anything that is not clear, or if you would like more information.
- Thank you for taking the time to read this information sheet. We hope you will find this information helpful.

Important things to know

- There are two parts to the research we are doing. The first part is the vitamin D screening study.
- At your routine Crohn's Disease out-patient appointment we will check your vitamin D levels with a finger-prick blood test and ask you some questions.
- The questions will be about things that can affect your vitamin D levels, such as your diet, taking vitamin supplements and your exposure to sunlight.
- This will take about 20-30 minutes in total.

Why are we doing the D-CODE study?

About half to three-quarters of people with Crohn's Disease may develop vitamin D deficiency (very low levels of vitamin D in the body). Vitamin D is very important in helping to maintain healthy bones. But research has found that for people with Crohn's Disease, having normal levels of vitamin D might also help to improve the symptoms of their disease.

The Vitamin D Screening Study will help us to:

- Understand what proportion of people with Crohn's Disease have vitamin D deficiency.
- Understand any specific factors that might contribute to vitamin D deficiency in people with Crohn's Disease.
- Identify people who may wish to join the second part of our research study.

Why have I been asked to take part?

We are inviting you to take part in this study because you are an adult patient at one of the hospitals taking part and have been diagnosed as having Crohn's Disease. We are inviting all patients who are eligible to join and not only people at any higher risk of developing vitamin D deficiency.

What will I have to do if I take part?

A member of the clinical team will talk to you first in more detail and you will be able to ask any questions that you may have. If you have had all of your questions answered and are happy to take part in this part of the study then you will be asked to sign a consent form to confirm you want to participate. You will be given a copy of the consent form and the information sheet to keep.

You will need to have a finger-prick blood test to check your vitamin D levels and answer some questions about your medical history, medications you take and answer questions about your diet and lifestyle.

We will write to you and your G.P. in about a week with the result of the blood test. If your vitamin D level is normal then you do not need to do anything else as your participation will be complete you are no longer eligible for part two.

If your vitamin D level is very low and you are eligible we may invite you by telephone to join the second part of our research study. We will give you more information about this part of the study if you are eligible to join.

If your vitamin D levels are very low and you choose not to join the second part of the study, or if you are not eligible to join, you should discuss this with your G.P. You will also find helpful information on the NHS Choices website https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/

Alternatively, you may ask for further information at your local health centre.

Timeline of visits

Screening is taking place for people who are attending their normal Crohn's Disease out-patient appointment at either the Queen Elizabeth Hospital Birmingham, Birmingham Heartlands Hospital or Good Hope Hospital.

We will aim to carry out the screening on the same day as your appointment for your convenience. However, you can return on a different day for this if you prefer.

What are the benefits and risks of taking part?

There should not be any risks involved in taking part in the Vitamin D Screening Study. Some people may find the finger-prick blood test uncomfortable. We need four large spots of blood for the test. If we find it difficult to get enough drops of blood from the first finger prick we may need to repeat it. We

will try to take the samples from the least sensitive part of the fingertip.

We hope that the results from the study will help doctors and patients in the future when making decisions about treatment.

Expenses and payments

There are no payments or expenses refunded for this part of the study.

Do I have to take part?

No, taking part is voluntary. The standard of care you receive now or in the future will be the same whether you take part or not.

What happens if I change my mind?

If you choose to take part you can also choose to stop at any time without giving a reason. You will receive the treatment and aftercare usually offered by your hospital.

We will use any study information collected up until the time you stop taking part.

Will my participation be kept confidential?

Yes. All information collected about you during the course of the study will be handled according to all applicable ethical and legal requirements. Your personal information will be kept strictly confidential and will only be accessed by people working on the study or working to ensure the study is being run correctly.

You will be allocated a study number, which will be used with your date of birth to identify you on each paper form. Your full name and date of birth will be included on your consent form but this will be kept at your hospital and a copy filed in your medical notes. The document that links you to your study number will be kept at your hospital.

It is very important that your G.P. is aware of your participation for your ongoing care. We will send a letter to your GP to let them know you are taking part and we will give the vitamin D result.

Your hospital team will collect information from you and your medical records for this research study in accordance with University Hospitals Birmingham NHS Trust instructions.

Your hospital team will use your name, NHS number, date of birth and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from University Hospitals Birmingham NHS Trust and regulatory organisations and the Liverpool Clinical Trials Centre (LCTC), part of the University of Liverpool, may look at your medical and research records to check the accuracy of the research study. Your NHS hospital will pass these details to University Hospitals Birmingham NHS Trust along with the information collected from you and your medical records. The only people in the University Hospitals Birmingham NHS Trust who will have access to information that identifies you will be people who need to contact you to discuss your vitamin D result or audit the data collection process. The Liverpool Clinical Trials Centre is helping to co-ordinate the study and analyse the results. To do this the LCTC will receive your study number and your date of birth, along with information from the study including medical information that is relevant to the study and the data collected during the study.

What will happen to the blood samples I give?

The finger-prick blood sample that you give will be sent to Sandwell and West Birmingham NHS Trust, City Hospital laboratory to be tested for your

vitamin D level. This laboratory will receive your study number, your date of birth and sex to enable them to return the vitamin D result to your hospital team. This sample will be destroyed after analysis and will not be used for any further research purposes.

What will happen to the results of the study?

The results of the study will be made available to the public, presented at conferences and published in medical journals so that we can explain to the medical community what our research results have shown. Confidentiality will be ensured at all times and you will not be identified in any publication.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with one of your hospital team who will do their best to answer your questions.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Every care will be taken in the course of this clinical study. However, in the unlikely event that you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS Trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints procedures should be available to you.

*Additional information

The study has been reviewed for scientific content by the National Institute for Health Research (NIHR) and the Health Research Authority, National Research Ethics Service Committee. Newcastle and North Tyneside 2 Research Ethics Committee has reviewed the study and given approval for it to take place.

University Hospitals Birmingham NHS Foundation Trust is responsible for managing the study. The day to day running of the study will be carried out by their D-CODE study team with support from the Liverpool Clinical Trials Centre (LCTC), part of the University of Liverpool, study Team.

University Hospitals Birmingham NHS Foundation Trust is the sponsor for your study based in the United Kingdom and will act as the data controller for this study. This means that they are responsible for looking after your information and using it properly. We will be using information from you and your medical records in order to undertake this study. University Hospitals Birmingham NHS Foundation Trust, University of Liverpool and the laboratories used in the study will keep information about you for 25 years after the study has finished.

Your rights to access, change or move your information are limited, as they need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at www.dcode-trial.co.uk.

Thank you for reading this information sheet.

Contacts for further information

If you would like more information or have any questions about the D-CODE Study please talk to:

Investigator: **Jane Fletcher**

Telephone: **0121 371 4561**

Or visit the website: www.dcode-trial.org.uk

If you wish to discuss the study with someone independent of the research team you can contact the local NHS Patient Advice and Liaison Service (PALS) at your hospital.

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The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

FUNDED BY

NIHR | National Institute for Health Research

University Hospitals Birmingham NHS Trust
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
Birmingham B15 2GW
Telephone: 0121 627 2000

D-CODE Vitamin D Screening in People with Crohn's Disease
Adult Consent Form

To be completed by the Researcher:

Site Name:			
Screening Number			
Participant Initials:		Participant DOB:	/ /

To be completed by the participant :

Once you have read and understood each statement please enter your initials in each box	**Initial**
Example: I confirm that I have read and understand the Participant Information Sheet.	*JS*
1. I have read and understood the information sheet for this study. I have had the opportunity to ask questions and have had these answered satisfactorily.	
2. I understand that participation is voluntary and that I am free to withdraw from the study at any time, without giving a reason, and without my care or legal rights being affected. I understand that in some cases further information about any unwanted effects of treatment may need to be collected by the study team.	
3. I understand that my data will be retained for up to 25 years from the end of the study at the hospital site, laboratory and at the Liverpool Clinical Trials Centre (LCTC) part of the University of Liverpool and will be stored in a confidential manner.	
4. I understand that relevant sections of my medical notes and any data collected during the study may be looked at by authorised individuals from the study team and those listed under *additional information (NHS Trust, Sponsor, LCTC and Regulatory Authorities). I give permission for these individuals to have access to my records.	
5. I agree to my GP being informed of my participation in the study.	
6. I agree to take part in the above study.	
7. I agree for my data on NHS hospital admissions and treatment to be collected for the purpose of this study and understand this will include both routine paper and electronic NHS health care records covering the study period.	
8. I agree to being contacted by telephone and post for the purposes of the study	
9. I agree to a copy of my signed study consent form being posted to me for my records	

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D-CODE Vitamin D Screening in People with Crohn's Disease

Adult Consent Form

To be completed by the Researcher:

Site Name:	
Screening Number	
Participant Initials:	Participant DOB: / /

Your **full** name (please print):	
Your signature:	Date:

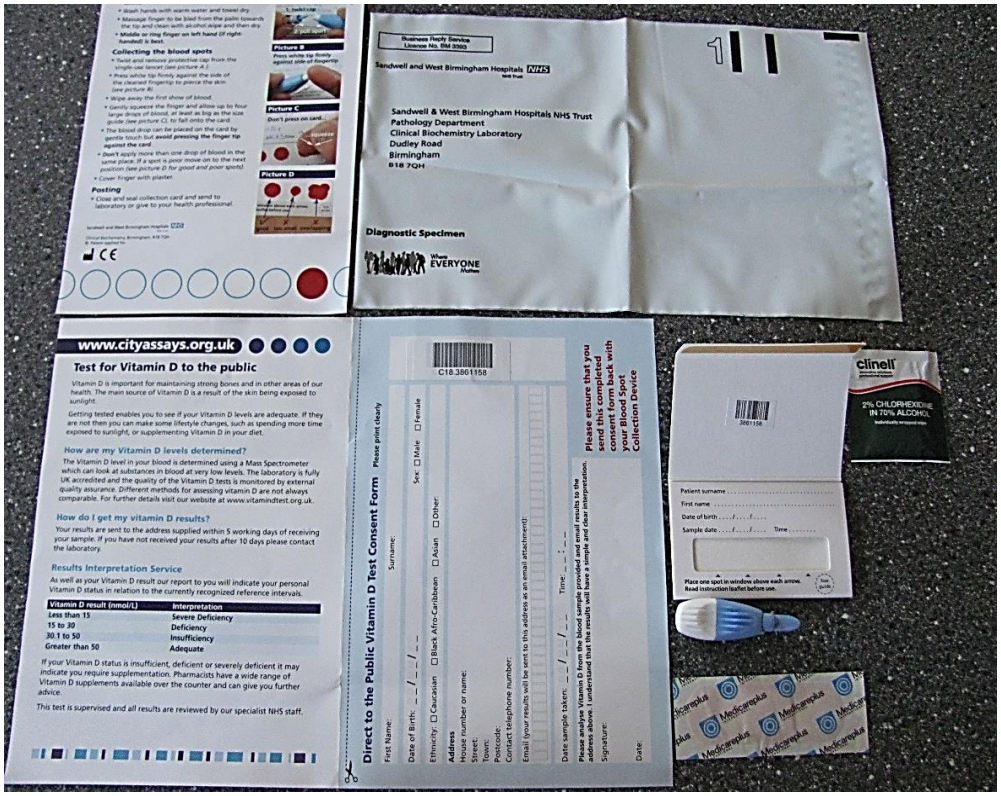
To be completed by the Researcher:

Researcher **full** name (please print):	
Researcher signature:	Date:

To be completed by the Translator (if used):

Translator **full** name (please print):	
Translator signature:	Date:

Appendix 8 Vitamin D Dried Blood Spot Sample Collection Kit



Postage paid sample return envelope

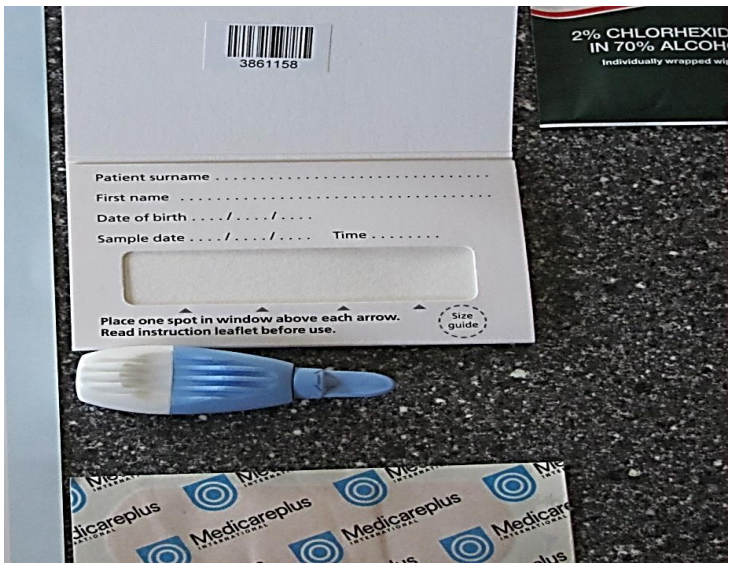
Cleansing wipe

Blood sample collection card

Lancet

Plaster

Sample collection kit information sheet and patient information return card



Appendix 9 Vitamin D Supplementation Trial Participant Information Sheet

University Hospitals Birmingham NHS Trust
Queen Elizabeth Hospital Birmingham
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Telephone: 0121 627 2000

D-CODE Feasibility Study

Vitamin D Supplementation in People with Crohn's Disease

Contents	Page

You are invited to take part in the D-CODE Study

- D-CODE is a study to compare two different doses of vitamin D capsules to treat vitamin D deficiency in adults with Crohn's Disease.
- The two treatment groups are:
  - vitamin D3 400iu, once daily for 24 weeks and
  - vitamin D3 3,200iu once daily for 12 weeks followed by vitamin D3 800iu once daily for 12 weeks.
- You have been given this information sheet as you might be eligible to take part in this feasibility study.
- Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve for you. Please take time to read the following information carefully and discuss it with friends or relatives if you wish.
- Taking part is voluntary. If you don't want to take part then you don't need to give a reason.
- Please ask a member of your clinical team if there is anything that is not clear, or if you would like more information.
- Thank you for taking the time to read this information sheet. We hope you will find this information helpful.

Important things to know

- This is a study involving about 50 patients.

- The aim is to determine if we would be able to carry out the D-CODE study across the country with a large group of patients. To establish this we must first carry this out with a smaller number of people.
- Adult patients with Crohn's Disease who have been found to have vitamin D deficiency on screening may be invited to join.
- Participants will be allocated to one of the two groups at random. The two different groups will get different doses of vitamin D capsules to treat their vitamin D deficiency.
- Participants will need to take their capsules for 24 weeks

Why are we doing the D-CODE study?

About half to three-quarters of people with Crohn's Disease may develop vitamin D deficiency (very low levels of vitamin D in the body). Vitamin D is very important to help maintain healthy bones. Recent research has found that for people with Crohn's Disease, having normal levels of vitamin D might also help to improve the symptoms of their disease. Despite this vitamin D levels are not routinely checked for people with Crohn's Disease.

There are many different doses and types of vitamin D available on prescription and over the counter but there is no standard treatment for vitamin D deficiency in Crohn's Disease.

About the study

The aims of the study are to find out:

- If it is possible to carry out the study with a large number of people to see which dose of vitamin D is best at treating vitamin D deficiency in people with Crohn's Disease
- How many people we would need in a large study to give us the most reliable results.

Study treatment

All participants will receive a vitamin called D3 (cholecalciferol). The capsules will be taken once a day by mouth. The capsules usually contain gelatine so are not suitable for vegetarians or vegans. For participants who observe Halal or Kosher we will confirm the source of gelatine with the manufacturer as required.

Study Procedures

We will need to take a number of blood tests and a stool sample from you to monitor the safety and effectiveness of the treatment. You will be given a sample pot to collect the stool sample. Blood tests will be taken at the start, after 12 weeks and then at the end of 24 weeks. Stool samples will be taken at the start and at the end of 24 weeks.

We will ask you to complete questionnaires at the start of the study and at the end of 24 weeks. We will ask you to keep a diary of when you have taken your vitamin D capsules each day. On your follow up appointments we will ask to see the diary and ask you to return any capsules you have not taken.

It is expected that each study appointment may take up to 40 minutes to complete. Appointments will be carried out at the hospital you usually attend for your Crohn's Disease follow up.

Duration

The total time you will need to be involved in the study is 28 weeks. Participants will take their capsules for 24 weeks in total. We will then do

one last follow up at 28 weeks. This follow up will be a telephone consultation and a short postal questionnaire.

Pregnancy
Pregnant and lactating women are not able to join the study. This is because the higher doses of vitamin D being tested are not suitable for those who are pregnant or breast feeding. You must tell us at the start of the study if you are pregnant or trying to conceive. We will ask women of child bearing age to take a pregnancy test before you join the study to be sure it is safe for you. We will also ask you to take contraceptive precautions while you are in the study. If you become pregnant during the study you must tell us immediately. In this case you would need to stop taking your vitamin D capsule but we would still wish to see you for your follow up appointments.

At the end of the study
At the end of the study if you feel that you have benefited from taking a vitamin D capsule we will write to your G.P.to suggest continuing this.

Why have I been asked to take part?

We are inviting you to take part in this study because you are an adult patient at one of the hospitals taking part and have been diagnosed as having Crohn's Disease and vitamin D deficiency on a screening blood test.

Expenses and payments

There is no payment for taking part in the study. However, we are able to reimburse standard travel and parking costs for your study appointments.

What will I have to do if I take part?

A member of the clinical team will talk to you first in more detail and you will be able to ask any questions that you have. If you have had all of your questions answered and are happy to take part then you will be asked to sign a consent form to confirm you want to participate. You will be given a copy of the consent form and the information sheet to keep.

How will I know which treatment I'm going to have?

In research studies, we often split patients up into groups to look at how different treatments work. Patients in one group get a different treatment than patients in another group. In the D-CODE study there are two treatment groups:

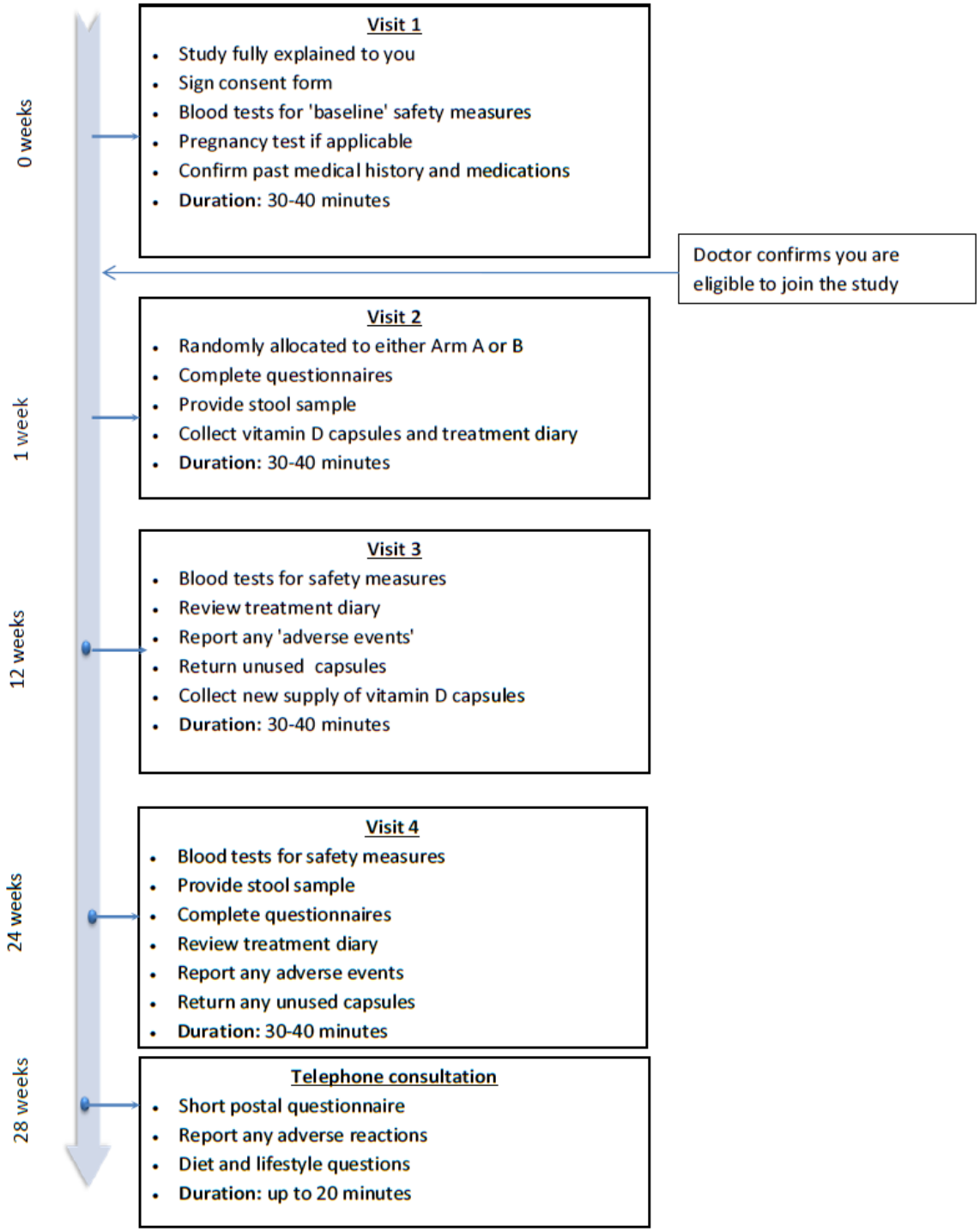
- One group (Arm A) will receive - vitamin D3 400iu, once daily for24 weeks.
- The other group (Arm B) will receive vitamin D3 3,200iu once daily for 12 weeks and then vitamin D3 800iu once daily for 12 weeks.

It is really important that each group in the D-CODE study has a similar mix of patients in it so we know that if one group of patients does better than the other, it is very likely to be because of the treatment and not because there are differences in the types of patients in each group.

We use a computer programme that puts patients 'at random' into one of the groups – you might hear this described as 'randomisation' or 'random allocation', but they all mean the same thing. Neither you nor your doctors choose which group you are in.

In the D-CODE study you are equally as likely to be in the group receiving the dose in Arm A as you are in the group receiving the dose in Arm B. Your healthcare team will let you know which group you are in as soon as possible.

Timeline of visits



What are the benefits and risks of taking part?

Benefits

We hope that the results from the study will help inform a large study that will help doctors and patients in the future when making decisions about treatment for people with Crohn's Disease. Both treatments have been shown to treat or prevent vitamin D deficiency, however we cannot guarantee that either treatment will make any difference to the symptoms of your Crohn's Disease.

Risks

The main risk of taking any vitamin D supplement is developing too much calcium in your blood (hypercalcaemia). Hypercalcaemia may also lead to calcium in your urine (hypercalciuria). This risk is classed as 'uncommon' but if this happened the main symptoms we would expect are:

- nausea
- vomiting
- passing large amounts of urine
- loss of appetite
- weakness
- apathy
- thirst
- constipation

For this reason your calcium blood levels will be checked at the beginning of the study to ensure they are normal. We will then check this at your 12 week and 24 week appointments along with other safety blood measures to ensure they remain within safe limits. We will contact you by telephone if we find your blood tests are not within the normal range

Rarely some people report developing a rash when they take a vitamin D capsules.

You must tell us immediately if you develop a rash or any of the symptoms mentioned. Contact numbers are given in this sheet on page 7.

If you are allergic to vitamin D or any of the ingredients you must tell us immediately.

You will need to have three sets of blood tests over the whole study duration. Some people may find these uncomfortable and there may be some bruising afterwards but samples will be taken by an appropriately trained person.

What are the alternatives for treatment?

There is no standard way of treating vitamin D deficiency in people with Crohn's Disease. If you would prefer to discuss alternative types of vitamin D supplementation or different doses please speak to your G.P. You will also find helpful information on the NHS Choices website https://www.nhs.uk/conditions/vitamins-and-minerals/vitamin-d/

Alternatively, you may ask for further information at your local health centre.

Do I have to take part?

No, taking part is voluntary. It is up to you to decide whether or not you want to take part. If you choose to take part you can also choose to stop at any time without giving a reason. The standard of care you receive now or in the future will be the same whether you take part or not.

What happens if I change my mind?

If at any point you decide to stop taking part in the study you will receive the treatment and follow up usually offered by your hospital. If you do decide to stop taking part we will ask you if you would like to:

- continue to complete follow up visits for the study or
- stop taking part with no more study visits.

The study team may be required to continue to collect some limited information about any side-effects you may have as a result of taking part in this study. This will only be collected if required by the regulatory authorities.

Will my participation be kept confidential?

Yes. All information collected about you during the course of the study will be handled according to all applicable ethical and legal requirements. Your personal information will be kept strictly confidential and will only be accessed by people working on the study or working to ensure the study is being run correctly.

You will be allocated a study number, which will be used with your date of birth to identify you on each paper form. Your full name and date of birth will be included on your consent form but this will be kept at your hospital and a copy filed in your medical notes. The document that links you to your study number will be kept at your hospital.

It is very important that your G.P. is aware of your participation for your ongoing care and safety. We will send a letter to your GP to let them know you are taking part.

Your hospital team will collect information from you and your medical records for this research study in accordance with University Hospitals Birmingham NHS Trust instructions.

Your hospital team will use your name, NHS number, date of birth and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from University Hospitals Birmingham NHS Trust, the Liverpool Clinical Trials Centre and regulatory organisations may look at your medical and research records to check the accuracy of the research study. Your NHS hospital will pass these details to University Hospitals Birmingham NHS Trust along with the information collected from you and your medical records. The only people in University Hospitals Birmingham NHS Trust who will have access to information that identifies you will be people who need to contact you to discuss your vitamin D result, results of other blood tests for safety monitoring or audit the data collection process. The Liverpool Clinical Trials Centre is helping to co-ordinate the study and analyse the results. To do this the LCTC will receive your study number and your date of birth, along with information from the study including medical information that is relevant to the study and the data collected during the study.

What will happen to the blood samples and stool samples I give?

Most of your blood samples and the stool sample will be sent to your usual hospital laboratory that is part of University Hospitals Birmingham NHS Trust to be tested.

However, two blood samples need to be analysed in specialised laboratories. For this reason Birmingham Heartlands Hospital laboratory (part of University Hospitals Birmingham) will measure a hormone called hepcidin in one sample. One sample will be sent to the Institute of Metabolism & Systems Research at the University of Birmingham. This sample will be used to look at different types of vitamin D in the blood in much more detail than can normally be seen. These laboratories will receive your study number, your date of birth and sex to enable them to return the results to your hospital team. Your blood samples and stool samples will be destroyed after analysis for this study and will not be used for any further research.

What will happen to the results of the study?

The results of the study will be presented at conferences and published in medical journals so

that we can explain to the medical community what our research results have shown. Confidentiality will be ensured at all times and you will not be identified in any publication.

What if there is a problem?

If you have a concern about any aspect of this study, you should ask to speak with one of your hospital team who will do their best to answer your questions.

If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.

Every care will be taken in the course of this clinical study. However, in the unlikely event that you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed and this is due to someone's negligence, then you may have grounds for a legal action for compensation against the NHS Trust where you are being treated but you may have to pay for your legal costs. The normal National Health Service complaints procedures should be available to you.

*Additional information

The study has been reviewed for scientific content by the National Institute for Health Research (NIHR) and the Health Research Authority, National Research Ethics Service Committee (REC). Newcastle and North Tyneside 2 REC has reviewed the study and given approval for it to take place.

University Hospitals Birmingham NHS Foundation Trust is responsible for managing the study. The day to day running of the study will be carried out by the D-CODE study team with support from the Liverpool Clinical Trials Centre (LCTC), part of the University of Liverpool, study Team.

University Hospitals Birmingham NHS Foundation Trust is the sponsor for your study based in the United Kingdom. This means that they are responsible for looking after your information and using it properly. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. University Hospitals Birmingham NHS Foundation Trust, University of Liverpool and the laboratories used in the study will keep information about you for 25 years after the study has finished.

Your rights to access, change or move your information are limited, as they need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at www.dcode-trial.org.uk.

Thank you for reading this information sheet.

Contacts for further information

If you would like more information or have any questions about the D-CODE Study please talk to:

Investigator: Jane Fletcher

Telephone: **0121 371 4561**

Or visit the website: www.dcode-trial.org.uk

If you wish to discuss the study with someone independent of the research team you can contact

the local NHS Patient Advice and Liaison Service (PALS).

This publication presents independent research funded by the National Institute for Health Research (NIHR) (and Health Education England if applicable) through a through a Clinical Doctoral Research Fellowship, ICA-CDRF-2017-03-083.

The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care

D-CODE - Vitamin D supplementation in people with Crohn's Disease

Adult Consent Form

University Hospitals Birmingham NHS Trust
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
Birmingham B15 2GW
Telephone: 0121 627 2000

To be completed by the Researcher:

Site Name:	
Screening Number	
Participant Initials:	Participant DOB: / /

To be completed by the participant :

Once you have read and understood each statement please enter your initials in each box	Initial
Example: I confirm that I have read and understand the Participant Information Sheet.	JS
1. I have read and understood the information sheet for this study. I have had the opportunity to ask questions and have had these answered satisfactorily.	☐
2. I understand that participation is voluntary and that I am free to withdraw from the study at any time, without giving a reason, and without my care or legal rights being affected. I understand that in some cases further information about any unwanted effects of treatment may need to be collected by the study team.	☐
3. I understand that my data will be retained for up to 25 years from the end of the study at the hospital site, laboratories and at the Liverpool Clinical Trials Centre (LCTC) part of the University of Liverpool	☐
4. I understand that relevant sections of my medical notes and any data collected during the study may be looked at by authorised individuals from the study team and those listed under *additional information (NHS Trust, Sponsor, LCTC and Regulatory Authorities). I give permission for these individuals to have access to my records.	☐
5. I agree to my GP being informed of my participation in the study.	☐
6. I agree to be contacted by telephone and post for the purposes of the study	☐
7. I agree to take part in the above study.	☐
8. I agree for my data on NHS hospital admissions and treatment to be collected for the purpose of this study and understand this will include both routine paper and electronic NHS health care records covering the study period.	☐
9. I agree to a copy of my signed study consent form being posted to me for my records	☐

Your full name (please print):			
Your signature:		Date:	

University Hospitals Birmingham NHS Trust
Queen Elizabeth Hospital Birmingham
Mindelsohn Way
Edgbaston
Birmingham B15 2GW
Telephone: 0121 627 2000

D-CODE - Vitamin D supplementation in people with Crohn's Disease

Adult Consent Form

To be completed by the Researcher:

Site Name:																			
Screening Number																			
Participant Initials:				Participant DOB:			/			/									

To be completed by the Researcher:

Researcher full name (please print):			
Researcher signature:		Date:	

To be completed by the Translator (if used):

Translator full name (please print):			
Translator signature:		Date:	

Appendix 10 Patient Reported Outcome Measures

IBDQ-32

PROMS were presented in booklets containing one version of the IBDQ-32 (with or without a stoma) and the EQ-5D-5L. The booklets were designed and developed by the data management team at the CTU.

To be completed before providing to patient

Can Vitamin D Supplementation in Patients with Crohn's Disease Improve Symptoms as an Adjunct Therapy: D-CODE Feasibility Study

Patient Reported Outcome Questionnaire Booklet 1

Screening Number: ☐☐☐

Randomisation number: ☐☐☐☐☐☐☐☐

Date of birth: D D M M Y Y

Time Point Eligibility ☐

Week 24 ☐

Please use this booklet if the participant does not have a stoma

Patient use only:

Please enter the date that you are completing the questionnaire:

Date completed: D D M M Y Y

Please hand in this questionnaire to the research team at your visit or return using the envelope provided.

For LCTC USE ONLY:

Date received: _____ **Date entered:** _____ **Entered by:** ☐☐

D-CODE Patient Reported Outcome Questionnaire: Booklet 1 V5.0 21/10/2020 Page 1 of 14

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from 1 through 7. Please read each question carefully and select the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

(1) ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE QUESTIONNAIRE (IBDQ)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

1. How frequent have your bowel movements been during the last two weeks? Please indicate how frequent your bowel movements have been during the last two weeks by picking one of the options from

1 BOWEL MOVEMENTS AS OR MORE FREQUENT THAN THEY HAVE EVER BEEN
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
5 SOME INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
6 SLIGHT INCREASE IN FREQUENCY OF BOWEL MOVEMENTS
7 NORMAL, NO INCREASE IN FREQUENCY OF BOWEL MOVEMENTS

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks have your bowel movements been loose? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

IBDQ

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with rectal bleeding with your bowel movements? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your underpants? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

IBDQ

32. How satisfied, happy, or pleased have you been with your personal life during the past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

To be completed before providing to patient

Can Vitamin D Supplementation in Patients with Crohn's Disease Improve Symptoms as an Adjunct Therapy: D-CODE Feasibility Study

Patient Reported Outcome Questionnaire Booklet 2

Screening Number: ☐☐☐

Randomisation number: ☐☐☐☐☐☐☐☐

Date of birth: D D M M Y Y

Time Point Eligibility ☐

Week 24 ☐

Please use this booklet if the participant has a stoma

Patient use only:

Please enter the date that you are completing the questionnaire:

Date completed: D D M M Y Y

Please hand in this questionnaire to the research team at your visit or return using the envelope provided.

For LCTC USE ONLY:

Date received: _____ **Date entered:** _____ **Entered by:** ☐☐

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

IBDQ-Stoma

INSTRUCTIONS FOR SELF-ADMINISTERED IBDQ

This questionnaire is designed to measure the effects of your inflammatory bowel disease on your daily function and quality of life. You will be asked about symptoms you have been having as a result of your bowel disease, the way you have been feeling in general, and how your mood has been.

There are two versions of this questionnaire, the IBDQ and IBDQ-Stoma. If you have a colostomy or ileostomy, you should complete the IBDQ-Stoma. Questions 1, 5, 17, 22, 24 and 26 are slightly different in each version. Be sure you have the correct questionnaire.

On this questionnaire there are 32 questions. Each question has a graded response numbered from 1 through 7. Please read each question carefully and select the number which best describes how you have been feeling in the past 2 weeks.

EXAMPLE

How often have you felt unwell as a result of your bowel problem in the past 2 weeks?

(1) ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

If you are having trouble understanding a question, **STOP** for a moment! Think about what the question means to you. How is it affected by your bowel problem? Then answer the question as best you can. You will have the chance to ask the research assistant questions after completing the questionnaire. This takes only a few minutes to complete.

Randomisation number: | | | | | | | | | Screening Number: | | |

Date of birth: | | | | | | | | |

QUALITY OF LIFE IN INFLAMMATORY BOWEL DISEASE FOR PATIENTS WITH STOMAS (IBDQ-Stoma)

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your ulcerative colitis/Crohn's disease or indeterminate colitis, the way you have been feeling in general, and how your mood has been.

1. How frequently have you had to empty your colostomy or ileostomy appliance during the last two weeks? Please indicate how frequent your stomal output has been during the last two weeks by picking one of the options from

1 AS OR MORE FREQUENT THAN EVER
2 EXTREMELY FREQUENT
3 VERY FREQUENT
4 MODERATE INCREASE IN FREQUENCY OF EMPTYING
5 SOME INCREASE IN FREQUENCY OF EMPTYING
6 SLIGHT INCREASE IN FREQUENCY OF EMPTYING
7 NORMAL, NO INCREASE IN FREQUENCY OF EMPTYING

2. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | Screening Number: | | |

Date of birth: | | | | | | | |

3. How often during the last 2 weeks have you felt frustrated, impatient, or restless? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

4. How often during the last 2 weeks have you been unable to attend school or do your work because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

5. How much of the time during the last 2 weeks has your stomal output been looser than normal? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

IBDQ-Stoma

6. How much energy have you had during the last 2 weeks? Please choose an option from

1 NO ENERGY AT ALL
2 VERY LITTLE ENERGY
3 A LITTLE ENERGY
4 SOME ENERGY
5 A MODERATE AMOUNT OF ENERGY
6 A LOT OF ENERGY
7 FULL OF ENERGY

7. How often during the last 2 weeks did you feel worried about the possibility of needing to have surgery because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

8. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

IBDQ-Stoma

9. How often during the last 2 weeks have you been troubled by cramps in your abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

10. How often during the last 2 weeks have you felt generally unwell? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

11. How often during the last 2 weeks have you been troubled because of fear of not finding a washroom (bathroom, toilet)? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

IBDQ-Stoma

12. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from

1 A GREAT DEAL OF DIFFICULTY; ACTIVITIES MADE IMPOSSIBLE
2 A LOT OF DIFFICULTY
3 A FAIR BIT OF DIFFICULTY
4 SOME DIFFICULTY
5 A LITTLE DIFFICULTY
6 HARDLY ANY DIFFICULTY
7 NO DIFFICULTY; THE BOWEL PROBLEMS DID NOT LIMIT SPORTS OR LEISURE ACTIVITIES

13. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

14. How often during the last 2 weeks have you had problems getting a good night's sleep, or been troubled by waking up during the night? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

15. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

16. How often during the last 2 weeks have you had to avoid attending events where there was no washroom (bathroom, toilet) close at hand? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

17. Overall, in the last 2 weeks, how much of a problem have you had with your stomal appliance filling up with large amounts of gas? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

18. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from

1 A MAJOR PROBLEM
2 A BIG PROBLEM
3 A SIGNIFICANT PROBLEM
4 SOME TROUBLE
5 A LITTLE TROUBLE
6 HARDLY ANY TROUBLE
7 NO TROUBLE

19. Many patients with bowel problems often have worries and anxieties related to their illness. These include worries about getting cancer, worries about never feeling any better, and worries about having a relapse. In general, how often during the last 2 weeks have you felt worried or anxious? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

20. How much of the time during the last 2 weeks have you been troubled by a feeling of abdominal bloating? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

21. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option from

1 NONE OF THE TIME
2 A LITTLE OF THE TIME
3 SOME OF THE TIME
4 A GOOD BIT OF THE TIME
5 MOST OF THE TIME
6 ALMOST ALL OF THE TIME
7 ALL OF THE TIME

22. How much of the time during the last 2 weeks have you had a problem with blood in your stomal output or blood from the rectum? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

23. How much of the time during the last 2 weeks have you felt embarrassed as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

IBDQ-Stoma

24. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom to empty your rectum, even though you have a stoma? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

25. How much of the time during the last 2 weeks have you felt tearful or upset? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

26. How much of the time during the last 2 weeks have you been troubled by accidental soiling of your clothing or bedding because of leaking from your stomal appliance? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

27. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

28. To what extent has your bowel problem limited sexual activity during the last 2 weeks? Please choose an option from

1 NO SEX AS A RESULT OF BOWEL DISEASE
2 MAJOR LIMITATION AS A RESULT OF BOWEL DISEASE
3 MODERATE LIMITATION AS A RESULT OF BOWEL DISEASE
4 SOME LIMITATION AS A RESULT OF BOWEL DISEASE
5 A LITTLE LIMITATION AS A RESULT OF BOWEL DISEASE
6 HARDLY ANY LIMITATION AS A RESULT OF BOWEL DISEASE
7 NO LIMITATION AS A RESULT OF BOWEL DISEASE

29. How much of the time during the last 2 weeks have you been troubled by nausea or feeling sick to your stomach? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

Randomisation number: | | | | | | | | | Screening Number: | | |

Date of birth: | | | | | | | | |

30. How much of the time during the last 2 weeks have you felt irritable? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

31. How often during the past 2 weeks have you felt a lack of understanding from others? Please choose an option from

1 ALL OF THE TIME
2 MOST OF THE TIME
3 A GOOD BIT OF THE TIME
4 SOME OF THE TIME
5 A LITTLE OF THE TIME
6 HARDLY ANY OF THE TIME
7 NONE OF THE TIME

32. How satisfied, happy, or pleased have you been with your personal life during past 2 weeks? Please choose one of the following options from

1 VERY DISSATISFIED, UNHAPPY MOST OF THE TIME
2 GENERALLY DISSATISFIED, UNHAPPY
3 SOMEWHAT DISSATISFIED, UNHAPPY
4 GENERALLY SATISFIED, PLEASED
5 SATISFIED MOST OF THE TIME, HAPPY
6 VERY SATISFIED MOST OF THE TIME, HAPPY
7 EXTREMELY SATISFIED, COULD NOT HAVE BEEN MORE HAPPY OR PLEASED

EQ-5D-5L

The EQ-5D-5L is suitable for patients with or without a stoma and so was included at the back of both versions of the IBDQ-32 questionnaire booklets.

Randomisation number: | | | | | | | | | Screening Number: | | |

Date of birth: | | | | | | | | |

EQ-5D-5L

Health Questionnaire

English version for the UK

Randomisation number: ☐☐☐☐☐☐☐☐ Screening Number: ☐☐☐

Date of birth: ☐☐☐☐☐☐☐☐

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

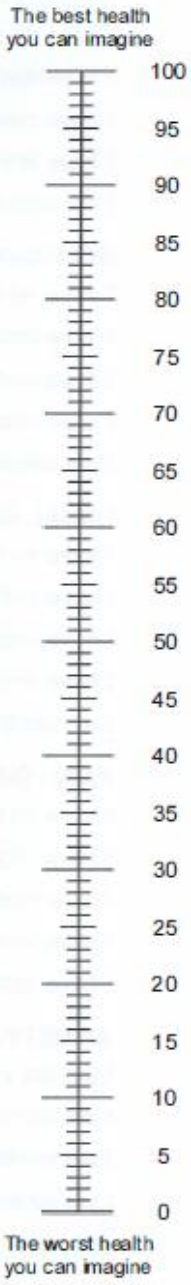
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Randomisation number: | | | | | | | | Screening Number: | | | |

Date of birth: | | | | | | | | |

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = | |



Participant Experience Questionnaire

To be completed before posting to patient

D-CODE

Can Vitamin D Supplementation in Patients with Crohn's Disease Improve Symptoms as an Adjunct Therapy: D-CODE Feasibility Study

Patient experience questionnaire

Randomisation number: | | | | | | | | |

Date of birth: | D | D | M | M | Y | Y |

Please provide this questionnaire to the participant at the week 28 visit

Patient use only:

Please enter the date that you are completing the questionnaire:

Date completed: | D | D | M | M | Y | Y |

Please return this questionnaire using the envelope provided.

D-CODE Patient Experience Questionnaire

Randomisation number | | | | | | | | |

Date of birth: D D M M Y Y

Thank you for participating in the D-CODE Feasibility Trial. We would value your feedback regarding your experience of being part of the research. Please take a few moments to respond to the two statements below regarding your experience.

Please circle one number on the scale. On the scale 1 indicates that you strongly disagree with the statement and 5 indicates that you strongly agree with the statement

	Strongly disagree				Strongly agree
I would be happy take part in another research study.	1	2	3	4	5
Comments: Please tell us more about your response:	*Please specify*				

	Strongly disagree				Strongly agree
I had a good experience of taking part in the research study.	1	2	3	4	5
	Please specify				

Thank you for completing the questionnaire

For LCTC USE ONLY:

Date Received: _____ **Date Entered:** _____ **Entered by** | |

Appendix 11 Trial Management Reflective Practice – Gibbs Reflective Cycle

PhD students would usually manage their own research, however, such student research is rarely a CTIMP, with all the additional regulatory commitments inherent in this. Sponsors and funders require a CTU to be involved in CTIMPs to ensure correct conduct of the trial and ensure all regulatory requirements are adhered to (Love et al., 2020). Therefore, it was not possible to carry out my research without the assistance of a CTU and without a specified trial manager (section 4.17.7).

The trial management role was new to me. Incorporating the role in to my PhD studies and conducting my research proved to be a significant challenge, with numerous pressures. However, it was also a valuable and unique learning experience that improved my overall knowledge and experience of the research process. There is a longstanding body of evidence related to experiential learning and the value of reflection in learning from experiences (Kolb, 2014, Boud et al., 2013, Schön, 1938). In a novel study of 9 reflective narratives in the practice of one osteopath, McIntyre et al (2019) found that reflective practice improved clinical reasoning. In a qualitative study of 59, 4th year nursing students the students expressed positive attitudes towards the value of their reflections in self-emancipation and improving their competence, although a small number (8%) experienced feelings of guilt from their self-critique (Hwang et al., 2018).

Given the uniqueness of my role within my own research, reflection on my experience was needed to fully explore and understand what I had learnt and how it will change my future research practice. Gibbs Reflective Cycle (Gibbs, 1998) formed the framework for my reflection, being a useful tool that has been used in many clinical and educational scenarios (Li et al., 2020, Tawanwongsri and Phenwan, 2019, Beam

et al., 2010). The model encompasses 6 key elements including description, feelings, evaluation, analysis, conclusion, and action plan.

Description

Trial management would usually be carried out by a trial manager who is a member of the CTU team and supervised by a Senior Trial Manager within the CTU. Trial managers are responsible for the CTU set up and day to day running of trials, with the role recognised as essential to effective planning, co-ordinating delivery and completion of a trial (Farrell et al., 2010). Such co-ordination involves working closely with the CTU based team, investigators, Sponsor, and study sites.

To ensure effective monitoring and management of the trial it was agreed that I would work within the CTU standard operating procedures (SOP) and perform as a member of their team. This required me to have an honorary contract with CTU and access to their trial manager training and systems as a usual member of their staff. I attended a 2-day induction programme at the CTU in May 2018, during which I completed a trial manager training needs analysis. I was given access to CTU IT systems, online training materials and other training events.

Feelings

Before I undertook the role, I did not know what to expect but I approached it with enthusiasm. The CTU team expressed surprise that I was taking on the role which caused me some concern regarding the scale of the task. However, by this point funding had already been agreed and I was unable to change my mind.

During my role at times, I felt confused and overwhelmed by the amount of administrative work required. At times the SOPs were detailed and helpful but at other

points there was the assumption of a certain level of knowledge that I did not have. I felt burdened by the constant need to organise and chair a range of monthly meetings.

The Senior Trials Manager had weekly remote meetings with me to support me and ensure I knew how to complete the necessary tasks. She also helped remind me of deadlines and aimed to oversee my work carefully. I felt that this must have been a burden to her, and that it would have been so much easier if one of their own Trial Managers was working on the study instead of me and this caused some feelings of guilt.

I feel that my undertaking the role of Trial Manager must have been a strain for the CTU team. However, they were supportive and helpful. I feel that overall, I performed my role reasonably well.

Evaluation

In Table 0-1 the positive and negative aspects of my experience as Trial Manager are explored with the resulting impact.

Table 0-1 Positive and Negative Impact of the Trial Manager Role

Positive	Impact
Gained a clearer, first hand understanding of the role of CTUs in the monitoring of research and the way CTU's operate as independent organisations.	Improved my under-pinning knowledge of research. This knowledge will assist me in the future design and conduct of my research.

Gained a clearer understanding of research processes and organisation, including safety reporting and management of serious breaches in clinical trials.	My new appreciation of the timescales involved in research will assist me to plan and schedule activities effectively. Where my future research involves a CTU, I will be in a better position to understand their perspective to ensure a clear understanding and a good working relationship.
Better understanding of the pros and cons of some data management elements, such as paper based CRFs versus electronic CRFs and the use of date validations in trial monitoring.	
Gained first-hand experience of the complexities of applying for regulatory approvals and maintaining approvals (making amendments, MHRA and REC annual reports etc)	
Convening multi-professional, multi-organisation meetings, organisation of meetings, chairing and minute taking.	A useful, transferrable skill that I will employ within my professional clinical role.
Learned more about version control of documents. This is particularly important within CTU operations to ensure the most current SOP and guidance is followed.	A simple but useful skill that I will employ within my usual clinical role when developing Trust wide clinical guidelines and procedures.
Opportunity to work with and learn from professionals I would not usually encounter, such as statisticians, data managers and other trial managers.	Built relationships for future collaborations.

Benefited from a supportive team at the CTU.	
Negative	**Impact**
Huge amount of new knowledge to learn, SOPs, working practices, IT systems	Overall CTU demands on my time have distracted me from my PhD studies and research time; meaning I feel that I have done less reading and been less involved in university activities as a result. My 'PhD experience' is diminished. I have been stressed and felt negatively towards the role at times.
Time consuming role, large amount of routine administration to be done in addition to my research and PhD work	
Stressful at times	
Practical difficulties with CTU being in Liverpool – travelling time to Liverpool carry out some Trial Manager activities e.g., Senior 'sign off' of the site files.	
Teleconference communication felt too remote	I felt isolated from the rest of the CTU team. However, this improved with the increased use and accessibility of videoconferencing/Microsoft Teams™ in response to the COVD-19 pandemic

Analysis

In considering some of the negative feelings towards my role as Trial Manager, I identified that the role itself was not the primary cause; rather it was the difficulty of undertaking the role while becoming an early career researcher. Trial Management

is a full-time role but in addition I discovered multiple challenges and new skills to learn in undertaking doctoral research. A qualitative study of 8 doctoral and postdoctoral students identified day to day challenges (frustration with unpredictability of research/scientific work) and long term challenges (organisation and institutional) faced by early career researchers. (Mcalpine and Amundsen, 2015). Katz (2016) describes the project management skills that early career researchers must acquire in order to manage their research effectively. In a survey of Israeli (n = 1013) and Western European (n=457) PhD students, Katz discovered that less than 5% had specifically acquired the skills needed to manage their project. In investigating the psychological health of 81 doctoral students, Barry et al (2018) found that key concerns included developing the expertise required to carry out their research and the challenges of general work procedures. In their study they found that participants had higher levels of stress and anxiety than the general population.

In addition to these challenges, I experienced time constraints as a particular obstruction that impacted both my Trial Manager role and research, despite being enrolled for full time study. The NIHR Clinical Doctoral Research fellowship comprises 80% research and 20% clinical time, i.e., 20% of my time was required to be spent in my normal clinical role and not research related. Thus, I was required to condense full time research into 80% of the time usually required, and maintain elements of my clinical role. Similar difficulties and tensions related to the duality of the clinical academic role have been discussed by other non-medical fellowship students (Newton and Fulop, 2017).

Nevertheless, my experience of being Trial Manager was generally positive and successful. This success must at least in part be attributed to the support I received

from the CTU team in enabling me to carry out my Trial Manager duties; and my supervisory team in recognising these pressures and supporting me during my fellowship. This level of support has been shown to be crucial in the success of many PhD students (Ahmed et al., 2017, Platow, 2012, Orellana et al., 2016). In a cross-sectional study of 408 PhD students, from 63 universities in 20 countries, supervisor supportiveness was the greatest determinant of student satisfaction with their PhD and progress (Dericks et al., 2019). Furthermore, student self-determination has been shown to be a key motivational and success factor (De Clercq et al., 2021). A cross-sectional study carried on in the Netherlands with 474 medical PhD students found that those with the highest motivational score were in the group with the lowest 'burnout' score (Kusurkar et al., 2021). Thus, these positive elements of my experience enabled me to view the Trial Manager role as a challenging but valuable learning experience.

Action Plan

I will use my newly acquired skills in my future research design, conduct and planning. I will continue to maintain links with the CTU team for future collaborations.

Conclusion

Undertaking the role of Trial Manager for my study was unnecessary and added pressure; particularly given that I was a novice researcher and carrying out all research elements myself. Despite this, it has been a valuable learning experience that has equipped me with unique skills and knowledge that I can take forward in to my clinical academic career. I do not think there is anything that could have prepared me better for the role as I had all the support possible from the CTU team, my allocated Senior Trials Manager, and my supervisory team. This experience has

demonstrated that, while it is feasible to carry out trial management in conjunction with undertaking all research roles, the dual role places the researcher under a considerable amount of added pressure. Clinical trials would usually have the support of several people including research nurses. This must be taken into consideration when calculating costs and making funding applications.