OSLO UNIVERSITETSSYKEHUS –HF RIKSHOSPITALET

Research Protocol

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1. Project title

Effect of FODMAP restriction on persistent GI-symptoms in coeliac patients

2. Introduction

The project targets a major disease group in Norway where there is an unmet and unresolved clinical need. The project is very patient-oriented and will contribute to clinical tools in management of coeliac disease. The research will immediately benefit the patient group.

Coeliac disease is a common condition, which affects at least 1-2 % of the population and the prevalence is increasing [2]. Many coeliacs worldwide are undiagnosed. This also applies in Norway, where Norwegian Coeliac Disease Association (NCF) has ca. 10 000 members, while it is expected that at least 50-100 000 people in the Norwegian population have the disease. There is no good disease registry on how many people have been diagnosed. Coeliac disease is characterised by small intestine is damage by an inflammatory process in the mucosa [2, 3]. This inflammation triggered by wheat gluten and similar proteins of rye and barley. Detection of tottering changes in tissue samples taken with gastroscopy, blood tests examining serum antibodies to the enzyme Transglutaminase 2 (TG2) or to Deamidated gliadin peptides (DGP) is necessary to detect the disease. It is important that these tests are taken while the patient eats gluten, because they will normalize on a gluten free diet. Follow-up of the patients is either done by serology or by serology and biopsy. Mucosal recovery is a treatment goal, persistent inflammation predisposes to malignant disease [4]. Serology is less sensitive than biopsy in this matter.

The symptoms of coeliac disease are only partially explained by the small bowel injury [2]. Micronutrient deficiency such as iron, folic acid and vitamin D as well as osteoporosis is common at the time of diagnosis. These deficiencies are not obligate nor typically for coeliac disease as they also exist in other diseases. Discomfort from stomach with flatulence, bloating, diarrhoea or constipation is very common in the disease but does not affect everyone. A feeling of constant tiredness and difficulty concentrating called "foggy brain" is also common. In addition to these characters is a plethora of associated diseases such as hypothyroidism, diabetes, infertility, arthritis and skin lesions. Patients with coeliac disease have increased mortality because of a certain cancer hazard. They are prone to lymphomas and adenocarcinomas, but the risk is reduced with treatment by gluten free diet [2].

2.1 Needs description

Treatment of coeliac disease

The treatment of coeliac disease is today a lifelong gluten free diet, although alternative treatment options are being developed [5]. A gluten free diet means a diet devoid of wheat, rye, barley and closely related cereals. This treatment provides in most cases good results. Monitoring and teaching by a clinical dietician are particularly important for coeliacs, and this practice group is invaluable. However, patients are dependent of gastroenterologists` and GP`s awareness of the disease, and there is a continuous effort to improve this knowledge.

Although treatment with gluten free diet usually gives good results, there are many patients who have continued ailments from their stomach or with their general health after they have started a diet [6-10]. This could be due to either failure to adapt to a really strict diet (compliance problems due to lack of knowledge or lack of motivation), or it could be symptoms compatible with, and caused by factors giving, what is referred to as “irritable bowel syndrome” (IBS). Data from US suggest this to affect 10-20 % of coeliac patients [8], whereas a recent Finnish study found that 23 % of long-term well-treated coeliac patients still had persistent gastrointestinal symptoms [10].

There have been no studies on persistent gastro-intestinal symptoms in celiac patients from Norway, but with our broad clinical experience from the patient group, we believe that the numbers are at least at this level in Norway. We specifically aim at investigating the impact of FODMAPon this frequent condition with persistent symptoms in coeliac disease patients on a gluten free diet.

Figure 1. Examples of foods rich in FODMAP. Photo: Øistein Horgmo

The FODMAP concept

The term is short for Fermentable Oligo-, Di-, Monosaccharides And Polyols (FODMAP); dietary carbohydrates and other substances that are relatively resistant to intestinal digestion and absorbtion and as a result they pass on to the large bowel where they meet a rich bacterial flora able to ferment these substances. FODMAP rich food includes certain cereals, fruits, vegetables and legumes, see figure 1.

As a consequence gas may be produced and water-flux to the bowel is increased. This is a physiological process [11]. In patients v hypersensitivity leading to patient discc as illustrated in Figure 2

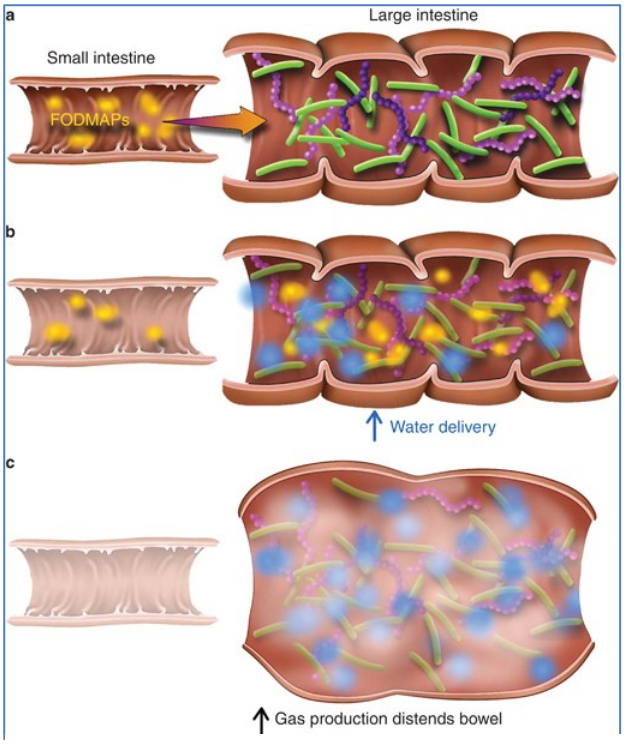

Figure 2. FODMAPs are poorly absorbed in the small intestine and can cause gas production and abdominal symptoms (with permission from [1])

Thus, FODMAP restriction has been proposed as a treatment for IBS and has been documented to be efficient in the majority of patients [14-17] In a recent study from Sweden, the effect of FODMAP reduction in IBS patients was seen, but not superior to alternative, standard treatment [18]. In clinical practice, FODMAP restriction is performed under the guidance of a clinical dietician. The first step is usually to record the patient's diet, exclude all food items with high FODMAP content from diet, followed by a structured re-introduction again under close guidance of a clinical dietician. FODMAP restriction done by patients themselves after written or online guidance lacks scientific support. FODMAP restriction has been included in the most recent NICE guidelines (NICE guideline CG61Irritable bowel syndrome in adults www.nice.org.uk).

A low FODMAP diet may also have impact on faecal microbiota. A recent study in IBS patients indicates that the responsiveness to a low FODMAP diet may be predicted by the microbiota profiles[19].

Although FODMAP reduction may play a role in patients with diet treated coeliac disease, there are no published studies addressing this topic. In fact, there is a huge knowledge gap and unmet clinical need for studying FODMAP in other patient populations than those suffering from IBS.

3. Hypotheses, aims and objectives

The overall aim is to improve dietary treatment of coeliac patients with persistent gastrointestinal symptoms in spite of a strict gluten free diet.

The project has two main objectives:

- **A)** To investigate the prevalence of persistent gastrointestinal symptoms and assess the amount of FODMAP in the diet of coeliacs on a strict gluten free diet. This will be done with a web-based quest back tool in collaboration with the Norwegian Coeliac Association.
- **B)** To perform a randomized, controlled trial in coeliac disease patients with gastrointestinal symptoms, comparing a low FODMAP glutenfree approach to an ordinary gluten free diet. This part of the project will also validate questionnaires and biomarkers for the assessment of gluten-free diet adherence.

In addition, the present project will provide unique biological materials for biobank and ongoing projects in our coeliac group. This is basic and translational research and is beyond the scope of this application.

The target audience is adult, Norwegian patients who have been diagnosed with coeliac disease, but despite strict gluten free diet experience considerable gastrointestinal symptoms.

The project is aimed directly at patients being treated in our public health system. The project is closely related to activities at OUH Rikshospitalet and the University of Oslo (Centre for Immune Regulation and KG Jebsen Centre for Coeliac Disease Research). It is appropriate to cooperate with other hospitals in the South-East Region for patient recruitment. Norwegian Coeliac Disease Association (NCF) will also be an important partner through their newsletter, website and Facebook group. We have recruited patients in other studies in this way so that we know this is a good approach [20-25].

4. Project methodology

4.1. Project design, method selection and analyses

Study A: Prevalence of persistent GI-symptoms in coeliac disease

Setting

We have a rather unique situation in Norway as the majority of patients with coeliac disease are or have been members of the NCF, and communication electronically and on social media like Facebook is widespread. This will give us the opportunity to perform an online survey as, in fact, has been done in Canada [26]. However, in the mentioned study they did not record on going symptoms. Persistent symptoms has more recently been evaluated in a Finnish study using direct patient contact and written formulas [10]. We propose to use a web-based technology to interact with as many coeliac disease patients as possible.

Design
A national cross-sectional study exploring prevalence of persistent symptoms in treated coeliac patients.

Patients
Members of NCF will receive e-mail invitation to participate in the online survey, as well open invitations in relevant social media that target the coeliac disease population. This method gives the opportunity to include a large sample, and since we aim to obtain the number of participants needed for study B, the number of participants in this part of the project will be unlimited within the following inclusion criteria:

- Biopsy verified coeliac disease patient, 18-75 years of age
- Strict gluten free diet for at least 12 months

NCF has approximately 10 000 members. We expect a 30 % response rate, and aim to include 3000 patients in this study.

Methods
We will use web-based questionnaires to survey gastrointestinal symptoms, health related quality of life and diet adherence by questionnaire.

For recording of gastrointestinal symptoms we will use a published and validated questionnaire that was originally developed for IBS purposes, the Gastrointestinal Symptom Rating Scale, IBS version (GSRS-IBS) [27]. We, and others, have found that this form is very well suited to evaluate the burden of disease and symptom level for IBS-like symptoms in treated coeliac disease, and it is suitable for measuring the effect of interventions [28]. The questionnaire is translated to Norwegian. FODMAP intake will be estimated by use of a questionnaire developed by Hatlebakk & co-workers [29].

In the current project we will employ recently developed disease specific quality of life forms. First, the Coeliac Disease Questionnaire (CDQ), a disease specific health related quality of life measure for adults with coeliac disease [30]. The form is translated into Norwegian, but has not been tested. Second, the Coeliac Symptom Index (CSI) was published by our collaborator in US, professor Dan Leffler at Harvard University, Boston [31]. This questionnaire is already translated and approved by the Harvard group. The project will include testing and validation of these disease specific tools for coeliac disease. Other relevant questions may add to the survey by NCF.

This study will also enable us to compare the collected information between CD patients with and without persistent GI-symptoms. Those patients who score high on the reported outcomes, will, as part of the survey, be invited to participate in study B.

Study B. A randomized controlled trial in patients with persistent GI-symptoms

Design
We will follow recommendations for design of clinical trials evaluating dietary interventions in patients with persistent functional gastrointestinal disorders [32]. A cross-over design has been carefully considered but is not possible as patients cannot be de-educated. A flow-chart of the study is given in Figure 3.

Patients
CD patients selected from study A, and willing to continue to study B

Inclusion criteria
- Coeliac patients (18-75 years) treated with GFD for at least 12 months
- Normal CD serology and duodenal biopsy (Marsh 0-1)
- Persistent gastrointestinal symptoms defined by GSRS-IBS score of 30 or more
- Strictly adherent to GFD
- Living less than 2 hours from study centre

Intervention
- Both groups will follow strict gluten free diet (GFD). The intervention group will in addition receive instructions on how to follow a FODMAP diet (LFD).

Endpoint
- Primary endpoint will be change in gastrointestinal symptoms measured by GSRS-IBS score.
- Secondary endpoints will be changes in biomarkers like serology and faecal microbiota

Adherence
Adherence to the diets will be monitored halfway in both groups. Assessment of dietary FODMAP and gluten intake will be obtained by 24-hour recall, which is a validated method for nutritional assessment in nutrition research [32]. Nutritional calculations will be done by the software Dietist Pro, which is implemented and used by dieticians at Oslo University Hospital, as well as in the other Nordic countries (www.kostdata.se/nb/dietist-net/dietist-net-pro).

Differentiated FODMAP calculations will be done by the software FoodWorks by our collaborators at the Monash University, Melbourne. To date, they are the only site that has a reliable FODMAP database based on food analysis.

Dietary assessment will also include evaluation of dietary adherence to the gluten-free diet by standardized dietician interview and by the coeliac disease adherence test (CDAT) [34]. There are few objective measures for diet adherence and the Norwegian translated CDAT version is not tested or implemented in Norwegian practice.

We will validate the CDAT questionnaire and recently suggested blood based tests for mucosal damage, the S-Intestinal Fatty Acid Binding Protein (S-IFABP) [35] and the faecal 33-mer peptide as a measure for gluten contamination [36]. Both these novel tests will be implemented at our clinical unit during 2018.

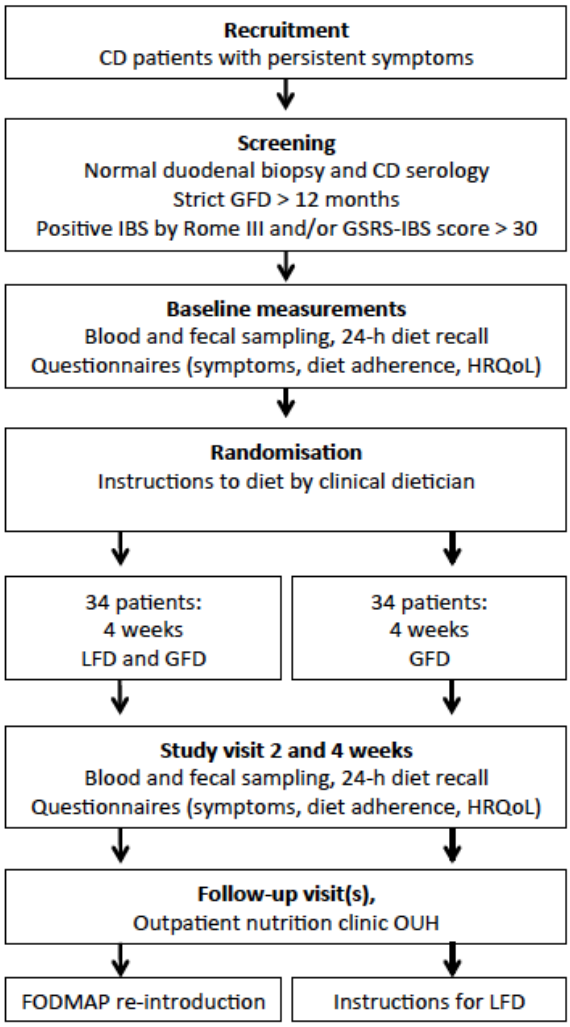

Figure 3 Flow-chart of study B.
LFD: Low FODMAP diet. GFD: Gluten free diet

All partisipants will be offered follow-up visits for re-introduction of FODMAPS (intervention group) or instructions for LFD (control group).

Power calculation:
The primary endpoint for measuring effect of the low FODMAP diet will be GSRS-IBS total symptom score. From previous studies with coeliac disease patients and non-coeliac gluten sensitivity persons we know that a clinical significant difference in symptom score is present when group means are 22,5 (SD 8) and 29,5 (SD 11), respectively (based on our unpublished results from on going clinical trial). With a power of 80 % and a significance level of 0,05 we will need 31 patients in each group. To account for 15 % drop out, we aim to include 72 individuals.

4.2. Participants, organization and collaborations

Project leader and main supervisor

Project leader, professor, dr. med. **Knut E. A. Lundin** is head of clinical education of medical students at Institute of Clinical Medicine, Faculty of Medicine, University of Oslo. He has a 20 % position as Consultant Gastroenterologist at Section for gastroenterology, Department of Transplantation Medicine, Oslo University Hospital. He has previously received funding from the Norwegian Research Council, the Extra Foundation as well as from Helse Sør-Øst. He has for the last 9 years been a senior faculty member of the Centre for Immune Regulation (CIR), led by

Professor Ludvig M. Sollid. CIR is a Centre of Excellence of the Norwegian Research Council, and is a FOCIS Center of Excellence. He is since 2016 group leader in KG Jebsen Centre for Coeliac Disease Research at the University of Oslo and Oslo University Hospital.

Lundin has published approximately 210 scientific papers including 120 original articles and 52 reviews and book chapters. His H-index is 50 and has 11,258 citations. He is main supervisor of Gry Skodje together with associate professor Christine Henriksen and Professor Marit Veierød. They have together supervised two clinical dietician students, who have completed the MSc thesis.

PhD student
We have received PhD grant for clinical dietician **Frida van Megen**. A few years ago, she finished her master degree in clinical nutrition: ”Sammenheng mellom inntak av FODMAPs og symptomer hos pasienter med inflammatorisk tarmsykdom i remisjonsfase som har irritabel tarm” with grade A. She experience with several of the methods to be used in the present study.

Co-workers
Associate professor and co-supervisor, PhD, MSc **Christine Henriksen** is a clinical dietician at Department of Nutrition, Institute of Basic Medical Science, University of Oslo. She has clinical experience and research experience with the patient group. She has published more than 20 scientific papers and is Editor in Norwegian Journal of Nutrition (**www.ntfe.no**). She has has an H-index of 11, has supervised 15 master students and is currently supervising two PhD students.

Clinical dietician **Gry Irene Skodje** has an MSc degree as a clinical dietician and is now employee at Unit for Clinical Nutrition at OUH Rikshospitalet. She has extensive clinical experience with patient group, she has both her own research and counselling experience on master level. She has been an Extra foundation PhD student and will complete her PhD degree during 2018.

Marit Veierød is Professor in Medical statistics at the Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo. She is also affiliated to the Department of Nutrition Research at the same institute. She has extensive supervising experience and is involved in numerous projects of clinical research. Lundin, Henriksen and Veirød have together supervised Skodje in her PhD project.

Jessica Biesiekierski is a current Post-doctoral Research Fellow with the Translational Research in Gastrointestinal Disorders (TARGID) group of KU Leuven in Belgium. In her PhD thesis from Monash University, Melbourne, Australia she investigated the effects of gluten and dietary carbohydrates in individuals who do not have coeliac disease. She has expertise in nutritional sciences, especially on large, randomised, double-blind placebo-controlled human dietary trials. She will help with the interpretation of the symptom assessment and FODMAP intake.

Eric de Muinck is a Post-doctoral Research Fellow with the Center for Ecological and Evolutionary Synthesis (CEES), a Norwegian Centre of of Excellence at the Department of Biosciences, University of Oslo. He has extensive experience in characterizing gut microbiotas and gut microbial ecology including cutting edge sequencing techniques (ref). The project leader has already co-authored paper with him[37].

The project will be done in collaboration with the Department of Gastroenterology at Haukeland University Hospital. There, Professor **Jan Gunnar Hatlebakk** is running an outpatient coeliac disease clinic where they also aim at investigating FODMAP restriction in coeliac disease patients. He will bring into the project his methods for assessing FODMAP intake by a short questionnaire.

In this project, we work closely with a research group at Monash University, Melbourne, Australia, with whom we already have published [38, 39]. This group is led by Professor **Peter Gibson** (clinical gastroenterologist) and Professor **Jane Muir** (clinical dietician). This group has pioneered the FODMAP concept, and will be responsible for the analyses of FODMAP intake from the diet.

We are at the moment running a large, collaborative project with this group, where we investigate the effect of gluten versus FODMAP challenge in individuals with self-perceived gluten sensitivity.

General secretary **Knut H. Peterson** in NCF will participate as the represent from the user group. He will be responsible for pre-testing the online questionnaire and patient support group contact.

Supportive infrastructure

The project will be run with infrastructure support already available within the project group. This includes

- Access to an endoscopy unit where the project leader has a 20 % position as a clinical gastroenterologist. The unit has a tradition for participating in studies like this for decades.
- Access to research engineers located at the endoscopy unit. These two engineers both have MSc degrees. They perform partly routine analysis, partly biobank tasks.
- Access to a study nurse located at the endoscopy unit. This nurse receives 1/3 of her salary from the Jebsen Centre where the principal investigator is group leader. She will aid in arranging patient appointments and in handling informed consent forms.
- Access to the locations at the Clinical dietician unit, Oslo University Hospital, Rikshospitalet for study visits. We will recruit at least two master students in Clinical nutrition.

KG Jebsen Centre for Coeliac Disease Research

The project will be performed within the recently started KG Jebsen Centre for Coeliac Disease Research (Centre director professor Ludvig M. Sollid, Professor Knut Lundin is one of five group leaders). This Centre was initiated in august 2016 and will be active till august 2020. Thus, it will cover the whole period for the current application. The Centre is located within the location of Institute of Immunology at OUH Rikshospitalet. The Centre has as its focus to study the immunobiology of coeliac disease, to improve diagnosis of coeliac disease and to investigate possibilities for non-dietary medical treatment options for coeliac disease. The current project not only fits very well within the clinical arm of the KG Jebsen Centre for Coeliac Disease Research but will also provide invaluable clinical material for the Centre's immunobiological activities. All clinical material in the current project will, with the informed consent of the participating patients, be deposited in the General biobank "Tarmsykdommer" where Lundin is the responsible clinician.

Clinical Dietician Unit at OUS

The project relies completely on access to an operable clinical dietician unit, the outpatient clinic (Ernæringspoliklinikken) at OUH Rikshospitalet. The study group is closely related to that clinic. One of the supervisors, Gry Skodje, has done the bulk of her PhD thesis work there. The unit is ideally situated at the Gaustad Campus; it is very close to the Jebsen Centre and the Endoscopy unit at the Department of Gastroenterology. Thus, all three units are located under the same roof.

4.3. Budget

The study will be done completely within the public health system and thus benefit from well-developed infrastructure. There will be no internal billing of hospital services as gastroscopy, blood tests or clinical consultations. The cost for Study Nurse is already covered by other sources (KG Jebsen Centre for Coeliac Disease Research). We here apply for the cost to a PhD student.

4.4 Plan for activities, visibility and dissemination

The time until the start of the project 01.06.2018 will be used for the completion of protocols and obtaining the necessary ethical approvals. The project is closely related to several of the projects we already have running in our group. Subproject with gluten provocation of treated coeliacs part of a South-East supported PhD project where PhD candidate will examine immune biological mechanisms of mucosal reaction to gluten. Since protocols are adjacent to each other, it is expected that all necessary approvals will be in place early. The following plan is submitted:

2018

- Completion of clinical report forms (CRF) for the two sub-studies
- Online Survey
- Planning and designing of the studies, application for REK, pilot testing, advertising for study participants
- Recruitment and clinical assessment of treated coeliacs with persistent symptoms
- Researcher training in the PhD education program

2019

- Recruitment, study conduct
- Analysis and writing subproject A
- Treatment and follow-up of patients in subproject B (expected to take the entire year)
- Researcher training in the doctoral program

2020

- Completion of subproject B
- Analysis of results and paper writing
- Writing frame report to the PhD degree, disputation

Suggested titles of the papers:

1. Prevalence of persistent gastrointestinal symptoms and FODMAP intake in patients with coeliac disease
2. Effect of FODMAP reduction in coeliac disease patients with gastrointestinal symptoms, a randomized, controlled trial
3. Validation of questionnaires and biomarkers for the assessment of gluten-free diet adherence

4.5. Plan for implementation

The findings in the study are expected to have immediate clinical impact that can be rapidly transformed to improve care of this large patient group. The project leader and the co-workers/supervisors (Skodje and Henriksen) all have active contact with local and national patient support groups. Lundin frequently holds talks at patient meetings, is a teacher at the Medical faculty at University of Oslo, and gives talks to clinicians. Skodje is member of the Scientific advisory board of the Norwegian Coeliac Disease Association. Henriksen is current editor of the Journal of the Norwegian Association of Clinical Dieticians. We will further communicate our findings in the Journal of the Norwegian Coeliac Disease Association ("Glutenfri").

5. User involvement

Participation of patients is of paramount importance for success in this project. As mentioned under chapter 4.5 we have broad contact with the patient group. The project will be done in close understanding and follow-up from representatives from the Norwegian Coeliac Disease Association. We have already established a Patient Advisory Board as part of our Jebsen Centre. We will seek to include the current project in the interaction with this Patient Advisory Board. Members of this board include the Secretary General of the NCF as well as the Director of Coeliac UK. For the current project, the representatives from the NCF: Knut H. Peterson will attend our bi-annual project meetings (PhD supervision will be regular and much more frequent).

6. Ethical considerations

The diet intervention is a short time restriction of a limited number of food items, and will do no harm to the participants. If the FODMAP intervention is superior to strict gluten free diet, the patients in the control group will be offered that treatment after the study is finished.

We will apply to Regional Ethical Committee (REK) for this project. We have a number of closely related applications that all have been approved by REK. We foresee that the current project also will be approved by REK. The project will further be posted on Helsenorge.no and

Clinicaltrials.gov. The biological material will be deposited in the approved general biobank "Tarmsykdommer" (REK ID number 2012/341).

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