Better treatment for Acute Sinusitis In primary health Care – BASIC

1. Relevance relative to the call for proposals

Acute sinusitis, one of the top reasons for primary care visits, is an important cause of morbidity, anxiety, lost time from work and school, and treatment costs (1). Acute sinusitis is also a leading cause of antibiotic treatment in primary care, although most patients do not benefit from antibiotic treatment (1). For the future, there will be a need to reduce the amount of prescribed antibiotics, due to the increasing challenges of antimicrobial resistance. Acute sinusitis appears to be the condition for which improved treatment and reduced antibiotic use is of particular importance.

We will test a novel treatment option for acute sinusitis, which is shown to be superior to systemic antibiotics in a pilot study; chloramphenicol eye drops to be applied to both eyes 8 – 10 times a day for a period of 2 – 4 days (2). To tailor the intervention, we will obtain data on the experience, health seeking behaviour, diagnostics and treatment of acute sinusitis, both through qualitative research, a nationwide survey, electronic patient record search and user group involvement. The patients in the trial will report own symptoms, and health registry data (former treatment, diagnoses, health encounters) will be obtained. To secure the safety of reducing antibiotic prescribing for acute sinusitis, health registry data on prescribing and complications that may arise from lack of antibiotic treatment will be analyzed.

Our project adresses the guidelines and principles set out in the call for proposal; The project adresses a **large patient group** which is **underrepresented in clinical research**. The project adresses the need to **develop clinical practice of tomorrow**, when antibiotics should not be used for self-limited conditions. The main study in the project is an **intervention study that combines clinical data with health registry data**, and the aim of the project is to produce results for **better and effectively targeted diagnostics and treatment**.

The project is in accordance with the BEHANDLING program plan; The project concerns the **municipality health care**, which still is a **research weak area**. We will **utilize national advantages** through the use of registry data based on unique identifiers, and study acute sinusitis **across different health care levels**. The project will probably be the first to **use a novel research network**, The Norwegian Primary Care Research Network (PCRN), thereby contributing to necessary **method development**. The project will to a high degree **incorporate user involvement**, both through interviews and surveys, and through the establishment of a user group for primary care research.

2. Aspects relating to the research project

2.1 Background and status of knowledge

Antimicrobial resistance and antibiotic use

The challenge of combating antimicrobial resistance is increasing worldwide. Antimicrobial resistance leads to suffering, prolonged illness, higher healthcare expenditures and even deaths. In Europe, an estimated 25.000 annual deaths are probably caused by multiresistant infections (3). The relationship between the use of antimicrobial agents and the appearance of antimicrobial resistance is well established through observational studies (4). Randomized controlled trials have proven this relationship to be causal at both the individual (5) and the community (6) level. One of the main strategies to withstand the challenges of antimicrobial resistance is therefore to minimize the use of antibiotics whenever possible.

In Norway, 85% of the total human sales of antibacterials in 2016 were prescribed in primary care, mainly by general practitioners (GPs) (7). Antibiotics prescribed for respiratory tract infections (RTIs) represent more than half of the prescribed antibiotics in Norwegian general practice (8).

Acute sinusitis

Acute sinusitis is a common condition, affecting about one in seven or eight persons each year (9). For most patients it is a self-limiting disease, often caused by a viral infection. Acute sinusitis may also be caused by a bacterial infection (in a minority of 2% of cases) (10). Regardless of cause, the condition most often resolves without antibiotic treatment. The incidence of serious complications of acute sinusitis is very low (2.5-4.3 per million people per year) (10). The main reason for antibiotic treatment is to relieve symptoms of purulent secretion and pain. A Cochrane review of 10 trials involving 2450

patients concluded that “there is no place for antibiotics for the patient with clinically diagnosed, uncomplicated acute rhinosinusitis (11). Antibiotics may shorten the symptom period with a number needed to treat to benefit of 18, but a higher number of patients receiving antibiotics experienced adverse events (number needed to harm: 8) (11). NICE guidelines recommend avoiding antibiotic prescriptions for patients with symptoms of 10 days or less (10). Norwegian guidelines recommend reserving antibiotics for patients with major symptom load and duration more than a week (12). Still, acute sinusitis is the condition that causes the largest volume of antibiotics for RTIs in Norwegian general practice, approximately 18%, which equals 10% of all antibiotic prescriptions in general practice (13). In the United States, acute sinusitis accounts for 15% to 21% of all antibiotic prescriptions for adults in the ambulatory setting (14). In the United Kingdom antibiotic prescribing rates for acute sinusitis remain as high as 92% (15), and are only slightly lower at 75% in Norway (13). Hence, there is a gap between the evidence that antibiotics have little or no place in the treatment of uncomplicated acute sinusitis, and the common practice leading to a vast amount of antibiotic prescriptions for this condition.

Diagnostics

Evidence-based guidelines stress the need that clinicians should distinguish presumed acute bacterial sinusitis from acute sinusitis caused by viral upper respiratory infections and noninfectious conditions, and to reserve antibiotics to those patients most likely to have a bacterial infection. Unfortunately the aetiology of sinusitis cannot be determined based on signs and symptoms alone, and additional tests are not easily applicable nor cost-effective in a primary care setting. Hence, GPs generally find it challenging to diagnose acute bacterial sinusitis (16). Patients with symptoms of sinusitis may consult their GP early during the course of illness and make demands for antibiotics [ref 3].

Treatment alternatives

Treatment alternatives other than antibiotics for acute sinusitis include saline nasal irrigation, use of nasal or oral decongestants, intranasal corticosteroids (INCS), antihistamines, mucolytics, analgesics and antipyretics (9). The use of decongestants and mucolytics is not recommended (9). INCS seems to be the most effective alternative to antibiotics, however the evidence is conflicting. One randomized, controlled trial found that INCS was superior to both antibiotics and placebo in improving symptom score (17). However, in another study, neither antibiotics nor INCS alone or in combination were effective in altering the symptom severity or the duration of the illness (18). Thus, it would be of great importance to find treatment options superior to systemic antibiotics. A Norwegian pilot study of 33 patients compared the use of chloramphenicol eye drops applied to both eyes 8-10 times a day with systemic antibiotics for sinusitus-like symptoms (2), and found a statistically significant difference in days before clear improvement in favor of the eye drops (3.7 vs 5.0 days). Chloramphenicol eye drops are topical antibiotics to be installed in the conjunctiva several times a day, ordinarily to treat conjunctivitis. The eye drops enter the nasal cavity through the nasolacrimal duct, and the proposed mechanism of action is inhibition of the growth of bacteria in the nasal cavity, or dissolvement of a potential blockage obstructing the sinus drainage tract (2). Topical antibiotics are associated with a lower risk of antibiotic resistance and adverse effects than systemic antibiotics (19).

The patient view

Acute sinusitis is a painful condition.

For RTIs, patients health seeking behaviour and doctors prescribing behaviour seem to have about equal effect on the amount of consumed antibiotics (20).

Antibiotics use and complications

Since 2012, the use of antibiotics has decreased by 21% in Norway. This is the fastest and largest reduction in antibiotics use since the drug was introduced in Norway. It is not known how the reduction is distributed for the different diagnoses, but there is reason to assume that the use has decreased for sinusitis. The reduction is probably a consequence of measures taken by the health authorities, which has a target of 30% reduction in the period 2012-2020 (21). A possible side effect of this wanted reduction is an increase in complications from untreated infections.

2.2 Approaches, hypotheses and choice of method

We hypothesize that chloramphenicol eye drops are superior to systemic antibiotics in controlling sinusitis-like symptoms in primary care, and reduce the amount of consumed systemic antibiotics.

We intend to test this hypothesis in a placebo-controlled, double-blind, pragmatic three arm randomized controlled trial. We aim to conduct a pragmatic trial with inclusion of patients in general practice, with eligibility criteria using clinical diagnostics and no use of computed tomography (CT) or ultrasound, mimicking real-life, first encounters for sinusitis-like symptoms in general practice. As treatment of sinusitis mainly is symptomatic treatment, we will use patient reported outcomes. Pragmatic (or effectiveness) drug trials are highly relevant in the general practice setting, exploring how an intervention works in a real-world setting. The pragmatic attitude favours design choices that maximise applicability of the trial's results to usual care settings for a wide range of participants (22). Choosing to conduct a pragmatic trial has implications for the trial design and affects the choice of eligibility criteria, recruitment strategy, setting, follow-up, and the relevance of the primary outcome and analysis of data. Although blinding is not a prerequisite in pragmatic trials, we chose to blind both patient and GP, as chloramphenicol is an untested drug for acute sinusitis.

Tailored inclusion criteria and intervention

The inclusion criteria in earlier RCTs on acute sinusitis treatment in primary care are highly heterogenous, and it is questioned whether included patients actually have acute bacterial sinusititis, acute viral sinusitis or common cold (23). However, it is impossible to distinguish between these conditions based on signs and symptoms alone. We intend to improve the treatment of patients currently being prescribed antibiotics for acute sinusitis, which means that we need to know how such patients actually are diagnosed in primary care, and how the decision to prescribe antibiotics is made. We hypothesize that gathering data from a large sample of GPs, made available through the new PCRN, will produce information of vital importence for tailoring the inclusion criteria and the intervention, and that this novel method will increase the applicability of the results in primary care.

Registry data in RCTs

Reduced antibiotics use and risk of complications

The positive effect of antibiotic stewardship is mainly at a societal level, and in a long time horizon. It is ethically troublesome to implement treatment options that increase the risk of complications for an individual patient in the present, in order to decrease the risk of illnesses related to antibiotic resistance for someone else in the future. For practical reasons, RCTs on infections are seldom powered to detect rare complications. In Norway, there are numerous high quality health registries, comprising data on close to all PHC visits, prescriptions, secondary care visits, hospital admissions and deaths, making it possible to detect changes in incidents of even rare complications. Changing incidence of complications associated with fluctuations in antibiotics use have been analyzed in other countries. We hypothesize that by combining and analyzing different longitudinal population-wide registries, we will be able to calculate the safety of reducing systemic antibiotic use for acute sinusitis.

The public' and patients point of view

The public's point of view. Primary care is characterized by easy access, patient centeredness and continuity of care. The easy access results in the GP consulting with patients that have chosen to come themselves, based on their ideas, concerns and expectations. As previously shown, the large variation in antibiotics use between Norwegian municipalities is about equally explained by inhabitants' consultation rates and GPs' prescription rates. It is therefore vital to understand why symptomatic persons chose to be patients; ie visit their GP. Also, the inherent patient centeredness and continuity of care in primary health care highlights the need to make sure that inventions are acceptable among both patients and general practitioners.

The Norwegian Primary Care Research Network (PCRN)

PCRN is granted funding from the Norwegian Research Council and will be established from year 2018 onwards. The objective of this research infrastructure is to provide a foundation for high quality primary care research in Norway, by facilitating identification and recruitment of primary care patients to clinical studies and by increasing the power and predictability of these studies. The PCRN will give wide access to eligible primary care patients for clinical research. The coordinating node of the research network will be located at the University of Bergen, with four regional research networks at Uni Research Health, the

University of Oslo, NTNU, and the University of Tromsø. Each regional network is planned to include from 15-30 clinical practices and actively support these clinics during data collection. In total, 300 GPs will be associated with the PCRN, covering around 6% of the general population. In this study we plan to use the secured IT infrastructure (24) provided by the PCRN. We will utilize the PCRN both in 1) a strategic selection of patients with varying experience with acute sinusitis, 2) an electronic patient record search and data collection on current diagnostics and treatment of acute sinusitis, and 3) recruitment of patients who present with sinusitis-like symptoms. We hypothesize that the PCRN will be an effective tool to carry out large and complex research projects in primary care, and that this project will contribute to method development regarding the use of PCRN.

3. The project plan, project management, organisation and cooperation

The project will contain three work packages.

Work Package 1 – Patient and prescriber views

The main aim of this work package is to explore sinusitis patients' attitudes, experiences, self-management, reasons for health encounters, and acceptability of eye drop treatment, and GPs' attitudes and reasons for antibiotic priscribing, and acceptability of eye drop treatment for acute sinusitis. The results will guide the development of the intervention in Work package 2, and will in addition provide neccessary knowledge for implementing antibiotic stewardship initiatives in primary care.

Qualitative study 1 – patients

Design: Qualitative individual in-depth interview study

Material: Individual in-depth telephone interviews with 15-30 patients with varying experience with acute sinusitis.

Recruitment: We will perform an automatic and anonymous electronic patient record search through The Norwegian Primary Care Research Network, and select patients with various experience with acute sinusitis the previous five years, ie patients with no, one or multiple contacts for acute sinusitis the previuos 5 years. The patients will remain unidentified for the project group, while the patients' GP will be asked to invite the patients to take part in a telephone interview. Patients consent to the research team, who then contacts the patient for interview.

Interview guide: We will develop an interview guide focusing on attitudes, experiences, self management and reasons for health encounters for sinusitis symptoms.

Analysis: Interviews will be recorded digitally and transcribed. The texts will be analyzed using the steps decribed as Systematic Text Condensation (25).

Qualitative study 2 – GPs

Design: Qualitative focus group interview study

Material: 5 focus group interviews with a total of 20-30 GPs.

Recruitment: We will recruit a purposeful sample of continous medical education (CME) groups, aiming at variety on gender, age and geography. In order to recertify as specialist in general practice, it is mandatory for the GPs to belong to a CME group.

Interview guide: We will develop an interview guide focusing on diagnostics and treatment of sinusitis-like symptoms.

Analysis: Interviews will be recorded digitally and transcribed. The texts will be analyzed using Systematic Text Condensation (25).

National survey

Design: National online survey among a representative sample of approx 2000 individuals.

Recruitment: We will use as platform the Norwegian Citizen Panel (NCP), a web-based survey of Norwegians' opinions toward important societal matters. The NCP is owned and maintained by the University of Bergen and is used exclusively for academic research purposes. It is a probability-based panel with participants drawn from the population registry.

Questions: We will perform 2 open ended and 5 closed questions on experience and attitudes regarding upper respiratory tract infections (URTI), health care seeking and self care. The questions will be prepared based on preliminary results from the qualitative studies and input from the user group.
Analysis: For the closed (numeric and categorical) variabls we will use standard quantitative methods (chi-square, t-test; categorical and linear multivariate regression). For the open-ended, textual responses we will use Structural Topic Modeling (26) to induce topics and analyse their co-variation with background variables.
Resources: Høye will be WP manager and supervisor. PhD student 1 will recruit and interview informants, and analyze the material. Tvinnereim will work on the survey, together with Høye and PhD student 1.

Work package 2 – Treatment

The main aim of this work package is to evaluate if a novel treatment option for acute sinusitis; chloramphenicol eye drops, offers superior symptom control compared to systemic antibiotics, and reduces the amount of consumed systemic antibiotics. The results, if positive, may contribute to a 10% absolute reduction in the total amount of systemic antibiotics prescribed in primary care.

We will develop and implement a double-blind, pragmatic, randomized controlled three-arm trial in Norwegian primary health care, making use of the newly established Norwegian Primary Health Care Research Network (PCRN). As a first step, we will perform a search in the electronic patient record of all GPs in the PCRN for the previous five years, gathering information on the diagnostics and treatment of acute sinusitis; earlier encounters for RTIs, earlier antibiotics prescriptions, symptom duration before encounters for acute sinusitis, prescriptions (antibiotics + others) for acute sinusitis, days off work, use of point-of-care-test, results of point-of-care-tests, symptoms, signs. In addition, we will take advantage of the results from the qualitative studies and the survey in WP 1. This will provide us with a comprehensive knowledge base on reasons for GP encounters, diagnostics and treatment of acute sinusitis-like symptoms in primary care. Based on this, while taking into account the user group's input, we will develop a tailored intervention. The framework of the intervention, described below, is therefore to be looked at as a preliminary plan. The trial will be conducted in accordance with *Regulation relating to clinical trials on medicinal products for human use*, including reporting of adverse events, supervised by The Norwegian Medicines Agency.
Recruitment: The PCRN is to recruit about 300 GPs to take part in the network. A sample of 100 of these GPs will be invited to recruit patients to the project. The GP will be payed for the extra time he/she uses on recruitment.
Inclusion (preliminary): Adult patients 18-65 years who present to the GP with sinus symptoms as main reason for encounter. More specific criteria will be developed based on mentioned knowledge base.
Exclusion (preliminary): Allergy or intolerance to any of the study drugs; received systemic antibiotic therapy within the past four weeks; prior sinus surgery; complications of rhinosinusitis; GP determines hospital admission is required; presence of a comorbidity that may impair patients' immune response; inability to speak and write in the language of consent; the participant is not able to complete the study protocol because of language barriers, intellectual disability, or other administrative issues.
Intervention (preliminary):
Arm 1: Systemic antibiotics, as according to The national guidelines for antibiotic treatment in primary care (12); Phenoxymethylpenicillin 0.66-1.3 gr x 4 for 7-10 days, after a minimum of 7 days symptom duration. Accordingly, if the patient presents after three days of symptoms, he/she is prescribed antibiotics, but asked to delay for four days, and start the antibiotic cure if no improvement
+ placebo eyedrops to be taken x8/day for 4 days, after a minimum of 7 days symptom duration.
+ patient leaflet on symptomatic treatment and advice on when to seek medical help.
Arm 2: Cloramphenicol eye drops to be taken x8/day for 4 days, after a minimum of 7 days symptom duration. Accordingly, if the patient presents after three days of symptoms, he/she is prescribed cloramphenicol eye drops, but asked to delay for four days, and start the cure if no improvement
+ placebo tablets x 4 for 7-10 days, after a minimum of 7 days symptom duration
+ patient leaflet on symptomatic treatment and advice on when to seek medical help.

Arm 3: No antibiotics/eye drops
Placebo tablets x 4 for 7-10 days, after a minimum of 7 days symptom duration
+ placebo eyedrops to be taken x8/day for 4 days, after a minimum of 7 days symptom duration.
+ patient leaflet on symptomatic treatment and advice on when to seek medical help.

Data:

Patient reported: Patients are to fill in a daily symptom- and treatment diary until symptom resolvement, maximum 28 days. We will use the SESAMe software (Survey Email Scheduling and Monitoring in eRCTs), a digital tool to improve data collection in randomized controlled clinical trials (27). The tool has been developed by researchers at The Department of General Practice, UiO. Included patients will get a daily reminder on their smartphone, and a link to the symptom diary. A printed diary will be available for patients without a smartphone. The symptom diary will include a validated symptom specific quality of life-instrument for adult acute sinusitis patients in PHC; the Sinonasal Outcome Test-16 (SNOT-16) (28). In addition, patients are to report any use of symptomatic treatment, adverse effects.

GP reported: Duration of symptoms at enrollment, symptoms, signs.

Laboratory data: C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).

Registry data: On inclusion, patients will be asked to report their Social Security number (*Fødselsnummer*). Based on this, we will obtain health registry data from The Norwegian Prescription Database, The Norwegian Patient Registry and The KUHR Database (Control and payment of health refunds), providing data on former antibiotics use, former encounters, operations/procedures and diagnoses in both primary and specialist health care.

Main outcome: In acute sinusitis, symptom severity and duration has proven to be of most importence for the patients. The main outcome will be days to symptom resolvement.

Secondary outcomes: Systemic antibiotic use, adverse effects, SNOT-16 scores at day 5 and 10.

Power calculation: Based on previous studies we assume that the mean duration of symptoms to be 10 days. Furthermore we assume that a clinical relevant difference in duration is 2 days, representing a 20% reduction. Based on these assumptions and a alpha of 0.05 and a beta of 0.10, and a cluster effect of 0.05, we need a minimum of 63 patients in each of the 3 groups. Taking into account the risk of drop-outs, we aim to include 75 patients in 3 groups, with a total of 225 patients. (SD = 3.0 days).

Resources: Høye will be WP manager. Lindbæk will be supervisor, Francis will be co-supervisor. PhD student 1 will work with the development of the intervention and the patient leaflets. PhD student 2 and postdoc will work with the development of the intervention, recruitment, follow up, analysis.

Work package 3 – Complications

The main aim of this work package is to evaluate the safety of reducing systemic antibiotic prescribing for acute sinusitis. The results will be crucial in order to implement stricter guidelines for antibiotic use in primary care, both nationally and internationally.

Design: Quantitative analysis of combined registry data

Material: To study negative consequences of decreased antibiotics use for acute sinusitis, we will draw on a number of longitudinal population-wide registers. The registers include unique personal identifiers (or an encrypted and linkable version) provided every individual at birth or immigration, enabling us to follow the same individual over time and across registers.

Data on acute sinusitis will be collected from several sources;

The Norwegian Health Economics Administration (HELFO) holds institutional data in the form of lists of the id of every GP and the id of every resident on each GP's list. Their database of reimbursement claims (KUHR) includes virtually all health related care covered by the insurance, conducted in Norway for persons not hospitalized or under the sole responsibility of the municipality (typically elderly care). Information includes id of claimant, id of patient, treatment and diagnosis codes. The coverage of KUHR is adequate for the last 10-15 years.

The Norwegian Prescription Database (NorPD) provides data on all prescription drugs dispensed outside of health institutions in Norway back to 2004. From this registry we will extract individual information on all dispensed antibiotics.

The Norwegian Patient Register (NPR) includes data on every patient in specialist health care in Norway back to 2008. From this data we will extract population-wide individual information on diagnoses, procedures and operations that may be attributed to complications of acute sinusitis (e.g. meningitis, orbital cellulitis, septicemia).
Analysis: For the period 2008-2019 we will estimate the incidence of acute sinusitis and sinusitis-like symptoms diagnosed in primary care, consultation rates and antibiotic prescription rates for these conditions, and incidence of complications that may be attributed to non-treated acute sinusitis.
The legal applications for data and the obtaining of data will be handled before the start of the project period, i.e. the data will be ready for analysis at project start.
Resources: Høye will be WP manager. Blix, Telle and Høye will be supervisors. PhD student 2 and postdoc will work with data handling and analysis.

Project management, organisation and cooperation

We will establish a steering committee for the project, with representatives from the University of Oslo, The Norwegian Institute of Public Health, The Norwegian Primary Health Care Research Network, Statistics Norway and the project management. The steering committee will meet twice a year. The role of the steering committee will be to facilitate the progression of the project through assistance, guidance and monitoring.
The project implies several transfers of informations and results between the different data sources and work packages; especially, the development of the intervention relies on the results from WP 1, the PCRN patient record search, and user group input. The research group will meet biweekly in order to ensure an effective flow of information.
The project will probably be the first RCT to use The Norwegian Primary Care Research Network. Both the electronic patient record search element and the patient recruitment element of the network will be utilized. The Department of General Practice, UiO, is one of the key partners in establishing the PCRN, and the project will draw benefits of the close relationship with the coordinating node at the University of Bergen and the regional staff at The Department of General Practice, UiO.
The project will make use of a novel tool to gather data from RCTs (SESAMe) (27), developed at The Department of General Practice; UiO. Likewise, the project will draw benefits of the close realtionship with the software developers at the Department.
WP 3 will make use of large datasets from different nationwide registries. The project implies network building and cooperation between the Department, Statistics Norway, and the Norwegian Institute of Public Health. Members of the research team have previously undertaken analyses on all the mentioned registries, and thus know the legal and ethical restrictions of the data well.
The members of the research group have experienc and expertice in project management, qualitative research, survey research, RCTs, handling and analysis of big data, and results dissemination and implementation;
Morten Lindbæk is professor at the Department of General Practice, UiO, and leader of The Antibiotic Center for Primary Care. He has been project manager and main supervisor of numerous RCTs on treatment of infections in primary care, among others penicillin vs broad spectrum antibiotics for erythema migrans (29) and NSAIDs vs antibiotics for acute cystitis. He has earlier performed an RCT on acute sinusitis, and is an international expert on the field, publishing editorials in the BMJ and JAMA.
Nick Francis is Clinical Reader in Primary Care at Cardiff University, a world leading department in clinical research in primary care. He has led and helped lead more than 20 studies addressing the use of antibiotics in primary care, including 12 randomised controlled trials.
Sigurd Høye is a postdoctoral researcher at The Antibiotic Center for Primary Care, UiO. Currently, he is project manager for his postdoctoral project and for a PhD project on antibiocs use in out-of-hours care. His expertice includes qualitative research, RCTs and implementation research in primary care.
Hege Salvesen Blix is professor at the School of Pharmacy, University of Oslo, and senior researcher at department of Drug Statistics, Norwegian Institute of Public Health. Her expertise is in the field of pharmacoepidemiology and pharmacotherapy, and she has been internationally involved in several projects on rational antibiotic usage.

Kjetil Telle holds a PhD in Economics from University of Oslo (UiO) and is Senior Research Fellow at the Research Department of Statistics Norway (SSB). He possesses detailed knowledge of the Norwegian health sector, and has written articles on e.g. health related issues based on population-wide registry data and advanced econometric methods and RCTs. His research has led to publications in top and leading journals, including *Rev Econ Studies*, *J Health Econ*, *Econ J and J Eur Econ Assoc.*
Endre Tvinnereim is Senior Researcher at the Uni Research Rokkan Centre for Social Studies and the Centre for Climate and Energy Transformation (CET) at the University of Bergen. His main research interests are quantitative text analysis in survey research and cross-national public opinion. Tvinnereim co-chairs the Climate and Environment section of the Norwegian Citizen Panel and has published in journals such as Nature Climate Change, Energy Policy and Global Environmental Change.
Anja Maria Lyche Brænd (MD) is PhD student at the Department of General Practice, UiO, and will earn her degree late 2018. Her research focuses on randomized controlled trials in primary health care.
We will recruit one PhD student to work with WP 1 and 2, and one PhD student to work with WP 2 and 3; both will be involved in the trial. It is vital for the Department and for The Norwegian Primary Health Care Research Network to build competence and experience among the PhD students in performing RCTs. The students will apply for admission at The National Research School in General Practice. The main supervisors for the PhD students will be Sigurd Høye (WP1/2) and Morten Lindbæk (WP2/3). Co-supervisors will be Nicholas Francis (WP1/2), Hege S. Blix (WP2/3) and Kjetil Telle (WP2/3). One of the PhD students will have a 3 months research stay at the University of Cardiff. We will recruit one Postdoc student to work with WP2. Supervisors will be Nicholas Francis and Sigurd Høye.

4. Key perspectives and compliance with strategic documents

4.1 Compliance with strategic documents

The Antibiotic Center for Primary Care (ASP) at The Department of General Practice, UiO, is a National center of competence with the purpose of promoting rational and limited use of antibiotics in primary care, thereby reducing the development of antibiotic resistance in Norway. One of ASPs core activities is to perform high quality clinical research on treatment options other than systemic antibiotics for common infections in primary care.
The department will be a partner in establishing the PCRN, which received funding from The Research Council of Norway in 2017. The project is in line with the intentions of the network; to provide a foundation for high quality primary care research in Norway.
The project adresses the aim set in the Norwegian inter-ministerial strategy plan on antibiotic resistance 2015-2020 (30): To perform studies on consequences of possibly too low antibiotic use.
The project is in line with the research needs concluded in the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (31);

- To know what factors determine whether acute rhinosinusitis (ARS) patients in the community consult with a doctor, pharmacist or self-manage without professional support?
- To show if the relative frequency of different symptoms and signs in ARS predict a differential response to different therapies, such as topical steroids and antibiotics?
- To determine biomarkers (e.g. CRP, procalcitonoin) that can predict acute bacterial rhinosinusitis or a clinically important response to antibiotics in ARS?
- To confirm whether topical nasal steroids can be the first-line treatment for ARS in Primary Care To show whether the provision of educational and information materials for patients improve outcomes of ARS and reduce non-essential antibiotic use?
- Large epidemiological data collection on the true incidence of complications in ARS, determining the role of Primary Care physicians in the detection and/or prevention of complications and whether complications of ARS relate to access to medical care?

4.2 Relevance and benefit to society

Faced with the global treat of antimicrobial resistence, this project will have a large influence on the amount of antibiotics consumed in primary health care, and thereby reduce the risk of morbidity and mortality associated with antibiotic resistance.

Norway is among the lowest antibiotic consuming countries in Europe, and has succeeded in reducing the antibiocs consumption in the last five years. Internationally, Norway is regarded as a country to look to and learn from when it comes to antibiotic stewardship. In addition, the extent and quality of Norwegian health registries gives a great advantage in antibiotic stewardship research. Therefore, Norway is in a unique position to perform clinical research on antibiotic stewardship in primary care. Research on the effect and safety of less resistant-causing treatment options for acute sinusitis will be of global interest and importance.

4.3 Environmental impact

The use of antibiotics is itself an enviromental threat. As the intervention will try out treatment options other than systemic antibiotics, the project in itself will reduce the amount of antibiotics that otherwise would have been consumed.
The project necessitates several flights for the project members. In order to reduce flights, we will perform web meetings when this is feasibel.

4.4 Ethical perspectives

The data, and especially the electronic patient record texts in WP2, are highly sensitive. We will follow the requirements of the national committee for research ethics. For confidentiality reasons, the project will ensure that researchers on a specific sub-project will not have access to more sensitive information than necessary. The data will be stored in The University of Oslo's Services for sensitive data (TSD).

4.5 Gender issues **(Recruitment of women, gender balance and gender perspectives)**

Both genders are represented in the research team. While the share of women is increasing in health education, and especially among physicians, the share of women in primary care research, and especially above PhD level, is low. When recruiting PhDs and postdoc students, women will be given priority if the competence is elsewhere equal.
Acute sinusitis is more common among women than men. This will be reflected in the project user group.

5. Dissemination and communication of results

5.1 Dissemination plan

Please see Dissemination plan in the electronic grant application form for details. In short, we will document our research in at least 12-15 papers in top and leading international scientific journals.

5.2 Communication with users

Please see *User involvement and anticipated benefits* document for details. In short, we will establish a User group (UG) consisting of patients, GPs and representatives from health authorities. The UG will meet twice a year in the early stage of the project, later once a year. The UG's opinions will have influence on the entire project.
GPs nationally and internationally will be the main target for the results of the project. We will seek to arrange sinusitis symposia at the biannual WONCA (World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians) World Conference in 2022 and at the annual WONCA Europe Conference in 2023.
ASP has established a platform for online courses and group meetings for GPs through the Research Council of Norway-funded ENORM project (32), reaching 50-70% of Norwegian GPs, and having a large impact on the participants antibiotic prescribing habits (33). This platform will be actively used to communicate the results from the project to Norwegian GPs. A follow up online course will be produced and offered to all GPs.

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