AbbVie

Medical Research /Research Plan [Insights number]

CROSS-SECTIONAL EPIDEMIOLOGICAL STUDY OF HCV INFECTION IN A DEFINED GEOGRAPHICAL REGION OF NORWAY

Product Name:	None
Type of Study:	Non-interventional Medical Research
Date:	06 OCT 2014
Biometrics:	Name and address of statistician (internal/CRO)
Sponsor(s):	AbbVie Norway

This study will be conducted in compliance with this research plan and all applicable regulatory requirements

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Amendment History:

List details of all research plan changes here when a new version of the research plan is produced.

Research Plan Version No.	Date issued	Author(s) of changes	Details of changes made
1			

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1. Project group

This study is an affiliate sponsored study and will be a collaborative project between AbbVie Norway, St. Olavs Hospital, Trondheim and the National Institute of Public Health.

Project group:

Clinical environment at St. Olavs Hospital: Raisa Hannula (MD, Department Head), Guro-Marte Gulstad (MD), Harald Otto Steinum (MD), Therese Svendsen (study nurse)

AbbVie Norge: Hege Edvardsen (Medical Advisor), Ann Kirsti Johansen (Scientific advisor, Affiliate Research), Jens Halvard Grønlien (MAM), Steinar Thoresen (Medical director)

Other external collaborators to the project: The Norwegian Institute of Public Health. In addition, LAR Trondheim (opioid substitution therapy system), The refugee healthcare centre and prison facilities within Trondheim. The interaction with these external collaborators will be coordinated by the clinical environment at St. Olavs Hospital.

2. Introduction

2.1. Global Epidemiology

Chronic hepatitis-C virus (HCV) infection is a global health problem with an estimated 185 million chronically infected individuals worldwide and 350000 people dying from this disease per year [1]. Among countries in which HCV has been studied, the prevalence varies markedly from one geographic region to another, with the highest prevalence so far identified in Egypt (15%) [2].

Based on newly published phylogenetic analyses seven major genotypes (GT) of HCV with altogether 67 subtypes are now reported [3]. The distribution of the different genotypes varies globally [2,3] with genotypes 1 through 3 found worldwide; genotype 4 predominantly found in the Middle East, central Africa, and Egypt; genotype 5 in South Africa; genotype 6 in Asia, and genotype 7 so far only isolated from an emigrant from Congo with region of endemicity remaining to be established (Figure 1, not including information on genotype 7) [2,3].

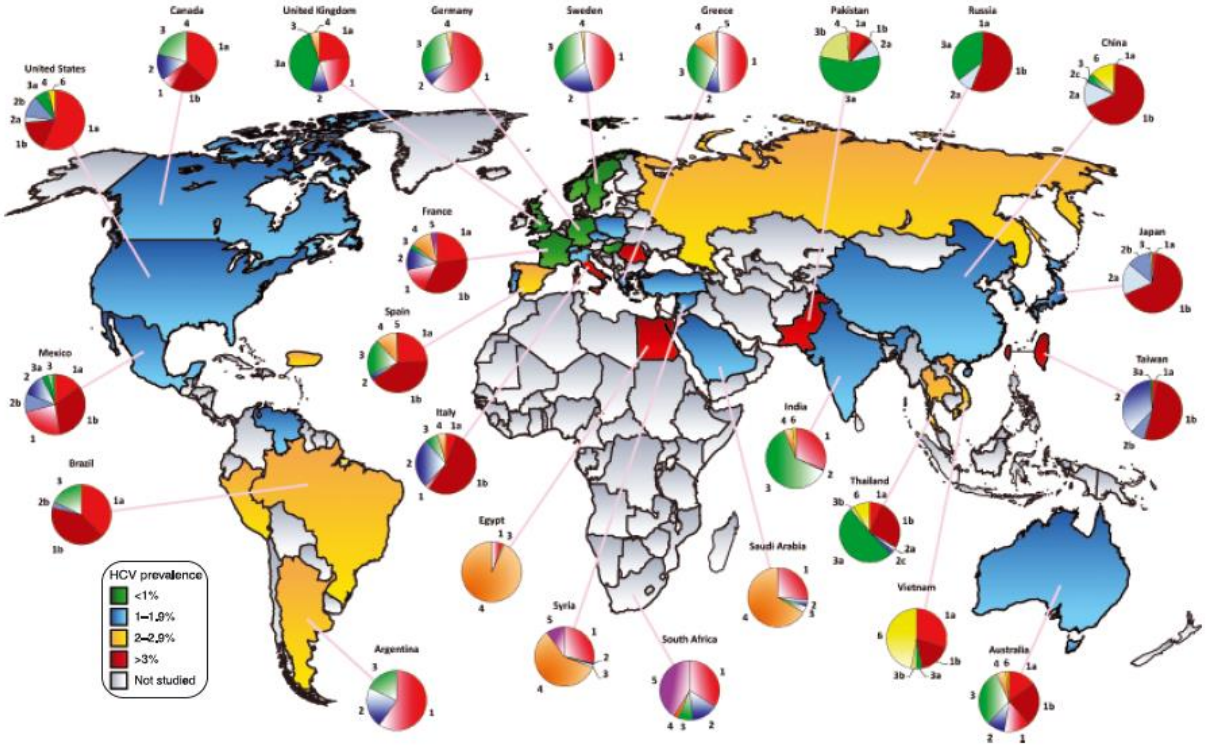

Figure 1. Global HCV-prevalence and distribution of HCV genotypes 1-6 (from [3])

2.2. Epidemiology in Norway

In Norway, the prevalence of HCV is estimated for the general population to be between 0.2- 0.7 % [4-8]. The main risk factor for HCV transmission is injecting drug use and among former and current injecting drug users (IDUs), the prevalence is estimated to be 81-88%, [7,8]. Globally the prevalence is 67% for IDUs [1]. For injecting drug users the risk of chronic HCV infection is increasing with number of years of drug usage, after 2-3 years of usage 50% are estimated to be infected with HCV [7,8]. Spread of HCV through blood transmission (contaminated blood and equipment) or through receipt of contaminated tissue and organs is rare as adequate procedures for screening of contamination have been in place since 1992.

Based on available data, overall genotype distribution within the Norwegian HCV population is estimated to be 50% genotype 3, 40% genotype 1, with genotype 2 and 4 comprising the majority of the remaining cases [7-9].

The Norwegian Institute of Public Health (NIPH) collects data on the number of reported HCV cases, geographic area, age and sex of reported individuals. The limitation of this database for contagious disease is that only information on serologically tested and diagnosed subjects are registered, and the database contains no information on genotypes or presence of active infection. Also, there is no information available on prevalence of HCV in the at-risk population or how many of the subjects are unaware of their HCV status. Screening procedures have been published and recommended by The

Norwegian Association of Infectious diseases and The Norwegian Association of Gastroenterology in The Norwegian Medical Association. Current available data from Norway is based on small studies or studies of selected subpopulations with little recent data being available [8]. There is therefore a need for more data to be able to fully describe the magnitude of the HCV prevalence in Norway [8].

2.3. Hepatitic C virus

The hepatitis C virus (HCV) was detected in 1989 and identified as the primary cause behind the infections former named «non-a/non-b» hepatitis (10). The virus is transmitted through contaminated blood and targets hepatocytes [10]. Possible routes of transmission are sharing of contaminated needles *e.g.* between drug users or vaccination without strict procedures regarding infection control, accidental injuries in health-care settings, sexual blood-to-blood contact, transmission of virus from mother to child during delivery and unsatisfactory infection control during tattooing or piercing procedures [1].

The virus is a small enveloped virus carrying a single-stranded, positive-sense RNA strand encoding 10 viral proteins necessary for replication and production of new viral particles (10).

Diagnostically a HCV antibody test is used to screen for infection. The test detects only exposure to HCV and cannot separate subjects with a former infection that has resolved from those with an active infection. A positive result must therefore be followed by a HCV RNA test that will indicate if the infection is still active.

2.4. Natural History of HCV Infection

HCV causes both acute and chronic infection. Acute infection is defined as the presence of hepatitis C virus within 6 months of exposure and infection with the hepatitis C virus [1]. After being infected 15-45% of the exposed individuals will clear the virus spontaneously while 55–85 % of newly infected persons develop a chronic HCV infection and will carry HCV in absence of treatment for the rest of their lives [1]. The infection is often asymptomatic but for individuals with chronic HCV infection the risk of developing cirrhosis is 15-30% within 20 years of infection [1]. Among individuals with cirrhosis the risk of developing hepatocellular carcinoma is approximately 2-4 % per year [1].

When harbouring a chronic HCV infection, known risk factors for progression of liver disease are: duration of HCV infection, male gender, excessive alcohol consumption, co-infection with HIV or hepatitis B virus (HBV), concomitant steatosis, obesity [11,12]. Infection with hepatitis C virus is linked to the development of insulin resistance (IR) and type 2 diabetes (DM). It is also shown that presence of DM and IR may accelerate progression of liver disease in patients infected with HCV. Finally, HCV-infected patients with IR and DM seem to have poorer response to an anti-HCV treatment regimen. Complications of chronic HCV infection include also a wide spectrum of generalized extrahepatic disease manifestations, which increase significantly morbidity and mortality. The comorbid conditions impact HCV treatment eligibility, tolerability and efficacy [13,14].

3. Study Rationale

Data on prevalence, including genotype distribution, within the different at-risk populations in Norway is restricted and to a large degree based on 1) data from Oslo and the surrounding regions, and/or 2) small populations and/or 3) from specific subpopulations only, such as active drug users. We hypothesize that proportion of undiagnosed HCV cases, genotype distribution of HCV and access to adequate health care, varies between the different population segments. To increase our knowledge of the epidemiology of HCV in Norway, our data will be collected from a region outside of Oslo. We aim to identify HCV infected individuals within high risk groups in the region of Trondheim; immigrants from HCV high endemic regions and former or active IDUs. For HCV infected individuals we will further collect information on state of infection and disease, HCV genotype, disease state and treatment history. This will provide a more complete picture of the disease burden within each patient group as well as information on the HCV disease burden in general outside of Oslo. Data collected in this study on the distribution of genotypes and subtypes is central for accurate estimation of the size of populations who could potentially benefit from emerging new therapeutic options such as all-oral therapy.

4. Study Objectives

Primary Objective

- To collect and describe data on HCV prevalence and genotype distribution in high risk populations (injecting drug users (current and former) and immigrants from high endemic regions) within the city of Trondheim

Secondary Objectives

- To describe characteristics of HCV infected individuals (such as sex, age, mode of HCV acquisition when known, time from infection or year of first drug injection, liver fibrosis stage, prior treatment and treatment outcome, current management of disease from the different patient segments) and their association with clinical parameters

5. Observational Plan

5.1. Study Conduct

This epidemiological study will be performed in a prospective cross-sectional design, non-interventional, single-country, single centre satellite-centre format, in the region of Trondheim, Norway.

Number of subjects, inclusion and screening procedure:

The study population will consist of approximately 1600 subjects above 18 years of age either with a history of injecting drug usage or being immigrants from a high endemic region identified as at-risk populations according to Norwegian guidelines for HCV:

“Injection drug users, subjects exposed to contaminated needles, subjects who have sniffed cocaine, HIV positive subjects, recipients of blood products given before 1992 in Western Europe, North-America, Japan and Australia and recipients of blood products from other countries regardless of time, immigrants from high endemic areas, patients with an elevated ALAT, subjects with accidental needle stick injury, patients receiving dialysis, subjects who have received non-professional tattoos, and persons who have had sexual intercourse with HCV-positive subjects”.

The study subjects will be enrolled from opioid substitution therapy (OST) clinics, outpatient clinics for drug users, prison centers and the refugee healthcare centre for immigrants (Figure 1A). The estimated number of subjects within the different systems is 300 in the OST system, 1000 regular visitors of the outpatient clinics for active drug users, 200 within prison facilities and 300 within the refugee healthcare centre . Due to overlap between the different systems the estimated number of unique subjects currently not being treated for an HCV-infection is 1600. The subjects will be contacted by the clinic through their respective institutions and offered the opportunity to participate in the study.. All subjects are given detailed written and verbal information about the study and sufficient time to ask questions before signing the consent form.

SoC at the above sites includes volunteer HCV testing. As a result, information on the presence of HCV antibodies will be available for the majority of the 1600 subjects. This information will be extracted from electronic patient files. For subjects with a negative HCV antibody test older than 4 months, a retest will be performed. If test remains negative, no further action is needed. Subjects invited to participate in the study will be documented on a separate subject list archived at St. Olavs Hospital. Eligible subjects not entering the study for whatever reason will be documented only by way of a subject number in a Data Recording Form (DRF) categorised as one of the following; does not speak the languages supplied, does not want to participate, available HCV serology data indicate no exposure to HCV.

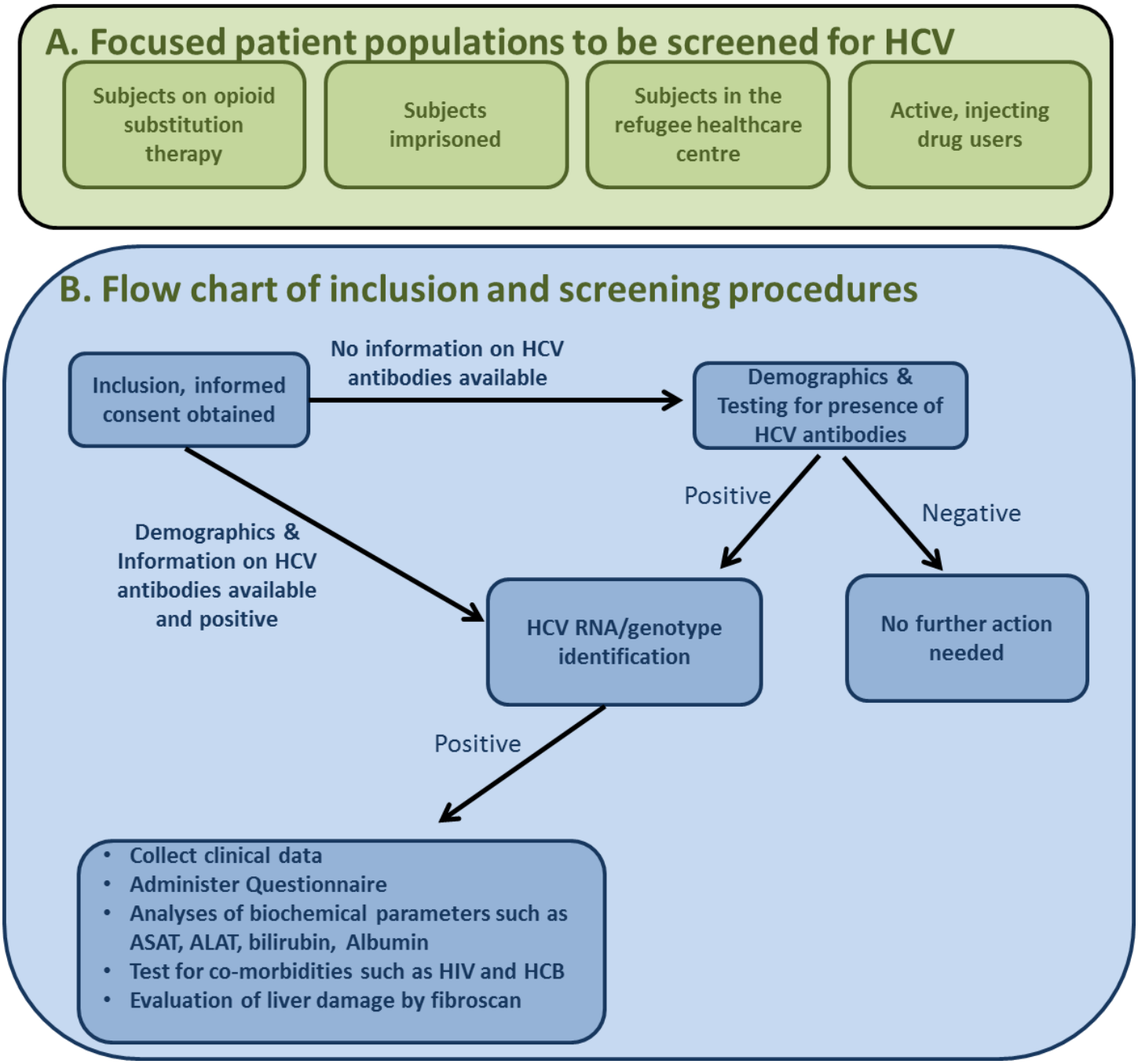

Figure 1. Overview of study populations to be screened (A) and flow chart of inclusion and screening procedures (B).

Procedures and diagnostic methods during screening will follow 'routine clinical practice' according to the screening recommendations for HCV in Norway published by The Norwegian Association of Infectious diseases and The Norwegian Association of Gastroenterology in The Norwegian Medical Association.
Subjects with a positive HCV antibody test will be included directly at the step of the HCV RNA (Figure 1B). Individuals previously not tested for HCV or with an existing HCV antibody test older than 4 months, will be tested for the presence of HCV antibodies. Following a positive result, a blood sample will be taken for

HCV RNA testing. If a positive HCV RNA test is obtained, the subject is included for full screening of liver disease related biochemical parameters and liver fibrosis measurements using a Fibroscan.

A total of 14 ml blood will be drawn. The samples will be destroyed at the laboratory according to standard practice once they have been analysed. The samples will only be used for diagnostic testing and the results will be sent to the study doctor at St. Olavs Hospital. Patient chart data of consecutively included subjects will be collected and documented in the Data Recording Form (DRF) from data available in the medical charts and laboratory reports. No patient identifiable information will be captured.
The sites will follow routine clinical practice if the screened subjects wish to be evaluated for treatment after completion of the study. Treatment procedures after completion of the study are not part of the protocol.

5.1.1. Patient Selection Criteria

Criteria for participant eligibility

Subjects attending a routine health check/visit, who fulfill the following selection criteria, can be included:

- Males and females turned 18 years of age with exposition to HCV
- Speak the language of the provided patient information/consent letters (Norwegian, English, Tigrinja, Somali and Arabic)
- Provide written informed consent to use and disclose personal health information

Subjects with the following criteria will not be included:

- Currently receiving HCV-specific antiviral therapy

5.1.2. Site Selection Criteria

There will be one primary research site. This is a medical centre experienced and specialized in the treatment of HCV for the region of Trondheim. The site represents a significant medical outpatient care unit for the treatment of HCV in this geographic region and will enrol the estimated number of subjects requested for screening in the study from the collaborative sites; refugee healthcare centre OST and prison system. Researchers will have access to the HCV population through visits to the different institutions.

5.1.3. Number of patients

Approximately 1600 subjects will be included in the first screening procedure of the study. We estimate that 250-300 patients will be included for the full protocol. This estimate is limited by current knowledge on prevalence being highly uncertain and a challenging study population. All patients with a positive anti-HCV test will be offered full screening including Fibroscan analyses. The study will be performed in Norway by the main site reaching out to at-risk subjects in surrounding institutions in Trondheim (prisons, refugee healthcare centre opioid substitution therapy settings, patients on the clinics waiting database for treatment etc.).

5.2. Study Duration

This is an epidemiological study. The study is planned to start first quarter of 2015 and the enrolment period will be approximately 8 months. At study start a designated study nurse will reach out to the satellite-centres to obtain informed consent. Collection of further samples will be started one site at a time. After enrolment is completed, data on referral to specialist will continue to be collected until database lock approximately Q1 2016. After all data is collected and transferred to electronic files the database will be locked before statistical analysis is initiated. Suggested start of statistical analysis is Q2 2016. A Study report will be submitted in final version to core team Q3 2016. Following approval of the study report from the core team, preparation of manuscripts will be initiated by end of 2016.

5.3. Description of Activities

Information collected in the study will be the following:

Visit 1 (after obtaining informed consent and assigning subject number):

- Subject demographics and characteristics (e.g. age, gender, nationality, ethnicity)
- Anti-HCV antibody test and HCV RNA quantitative test
- Health questionnaire; Subject awareness of HCV-transmission. Suspected mode of transmission. Estimated time of contraction or initiation of drug injection use. Has subject ever been an injection drug user. Is subject using stable opiate substitution and estimated years of injecting drug use. Prior anti-HCV treatment and treatment outcome. If subject wishes treatment evaluation after completion of the study.

Visit 2 (Subjects with a positive virus test for anti-HCV antibodies and HCV RNA test will continue with further screening):

- Vital signs (Blood pressure, height, weight and Body Mass Index)

- HCV genotype including subtype
- IL28 genotype
- HCV-viral load, HBsAg, anti-HBs, anti-HBc IgG, anti-HIV, anti-HAV-IgG, PT-INR, albumin, bilirubin, ALP, sodium, potassium, creatinine ferritin, ɣ-GT, CRP, calcium, leukocytes, hemoglobine, neutrophile granulocytes, *thrombocytes, cholesterol, triglycerides, HDL cholesterol, HbA1c, ALAT, AFP*
- anti-nuclear antibodies- (ANA), anti-mitochondrial antibodies, anti-smooth muscle antibodies) and free T4 and TSH
- Liver fibrosis stage (Fibroscan)
- Concomitant diseases (e.g. HIV, HBV, HAV)
- Clinical symptoms; (arthritis, palmar erythema, ascites, vasculitis/eczema, collateral abdominal veins, spider naevi). The subject will have the opportunity to be referred to the out-patient clinic for further management according to Norwegian guidelines.

5.4. Event Reporting

This is an epidemiological (cross-sectional) study. Therefore, it is not designed to identify or quantify a safety hazard related to an authorized medicinal product.

The study includes collection of blood samples in accordance with SoC and non-invasive measurements of liver fibrosis. In relation to collection of venous blood samples discomforts may include; pain, bruising at site of blood withdrawal, bleeding, inflammation, infection, temporarily redness of the skin and dizziness. The biological samples will be collected by a trained nurse and stored according to standard procedures. The samples collected will be in accordance with standard clinical procedures and the analysis will be performed by a certified laboratory.

For Prospective patient data

If a patient reports an adverse event to his/her healthcare professional (HCP) during the duration of the study, the event will be handled following routine clinical practice and, if applicable, reported as per local laws and regulations to the relevant regulatory authority and/or drug marketing authorization holder.

6. Ethics and Quality

This study will be run in compliance with local laws and regulations. Notification/ submission to the responsible Regional Ethical Committee, Health Institutions and/or Competent Authorities will be done as required by local laws and regulations (see Affiliate Agreement page). The standard of care (SoC) may vary from hospital/region to region, but follow the screening procedures recommended by The Norwegian Association of Infectious diseases and The Norwegian Association of Gastroenterology in The

Norwegian Medical Association. Data collected in this study is according to the recommended standard of care. Subjects recruited from the specified institutions (*e.g.* prisons and refugee healthcare centre) are considered consenting adults with the option to decline participation in the trial as any other participants in clinical trials. Subjects that will be included in this study from within the prison system or refugee healthcare centre may be considered to be in a fragile life-situation and the relationship between the institution teams and the subjects to be imbalanced with relation to power. The personnel at the satellite centres will therefore not have access to the questionnaire responses at the study consultation and only the study team at St. Olav Hospital will have access to this data before pseudonymity. As a consequence, we will ensure that the subjects understand that selecting not to participate will in no manner influence negatively on their further access to health care or other services of importance to their life situation. Written patient authorization to use and/or disclose his/her health data and informed consent will be obtained prior to patient inclusion. To maintain subject confidentiality, no demographic data that can identify the subject will be collected (e.g. initials, date of birth, name, and address), and only data listed in 'Description of Activities' will be collected. In order to protect the patient's identity, a unique number will be generated as pseudonym and assigned to each patient and related study records. The individual patient-ID number can only be accessed by the participating study doctor and the study team at St. Olavs Hospital.

Subject Authorization/Informed consent:

A signed study-specific informed consent will be obtained from the subjects before any study procedures are performed. The investigator or his/her representative will explain the nature of the study to the subject, and answer all questions regarding this study. This will be performed in the following languages: Norwegian, English, Tigrinja, Somali and Arabic. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by the subject, the person who administered the informed consent, and any other signatories according to local requirements. The subject will receive a copy of the informed consent form and the original will be placed in the site file at St. Olav Hospital. An entry will be made in the subjects' medical record that confirms that informed consent was obtained prior to any study-related procedures and that the subject has received a signed copy.

Data Collection

eDRF:

The centre will document patient data in electronic Data Recording Forms (eDRF). Examinations, diagnostic measures, findings and observations routinely performed in patients included in this study will

be entered by the researcher or staff under his/her supervision into the eDRFs provided by AbbVie, according to the research plan.

eDRFs will be provided to the site and subjects coded with a unique subject number. The participating site will be required to make entries to the eDRF at the latest 3 days after the subject visit.

Only data specified in the research plan will be submitted to the data management centre.

6.1. Source Documents

The investigator must maintain source documents for each patient in the study, consisting of medical records containing demographic data and diagnostic documentation and laboratory test data confirming HCV diagnosis.

6.2. Quality Assurance

The study's source data and consents forms will not be monitored.

7. Data Analysis Plan

7.1. Primary Endpoints

Analysis of the overall HCV-Genotype distribution and separately by subgroups defined by the parameters:

- Ethnicity
- Age (< 40, ≥40), Sex, IL28B
- Prior treatment status and prior treatment response
- Fibrosis stage, mode of infection and co-infections

7.2. Secondary Endpoints

Descriptive analysis of the overall treatment groups: naïve and prior treated, and separately by subgroups defined by the parameters within each treatment group:

- Ethnicity
- Age (< 40, ≥40), sex, genotype, IL28B
- Prior treatment response
- Fibrosis stage, mode of infection and co-infections

Analysis of the overall fibrosis stage groups and separately by subgroups defined by the parameters:

- Ethnicity
- Age (< 40, ≥40), sex, genotype, IL28B
- Prior treatment status and prior treatment response
- Mode of infection and co-infections

7.3. Plan for Statistical Analysis

Statistical analyses will be predominantly descriptive in nature. For continuous variables, measures of central tendency (mean or median) and dispersion (standard deviation (SD), minimum, maximum and interquartile ranges) will be presented. For categorical variables, the number and percentage of each category within an assessment will be calculated for non-missing data. Exact 95% confidence intervals (95% CI) will be provided for proportions. All results will be reported in aggregate by predefined patient groups (*e.g.* by genotype, injecting drug use, degree of liver damage as assessed by level of fibrosis) and may be stratified by key socio-demographic and clinical covariates. Univariate and multivariable regression models will likely be used to explore and determine the effects of putative predictors on patient group membership.

7.4. Sample Size Calculation

The study is exploratory in nature and we assume no pre-specified hypotheses about statistical significance and/or direction of correlations. There is thus no need for power calculation, but we assumed that a total of approx. 1600 subjects (from the area of Trondheim) are sufficient to provide statistically stable estimates of the correlations between specific characteristics observed.

Consecutive patient recruitment will be carried out within study centres. Overall recruitment will be overseen in order to achieve (at least approximately) a balanced distribution of the cohort regarding end-points to be analysed.

8. Final Report and Publications

The data generated in this study will be summarized in a project report and found the basis for scientific publications. A suggested outline of publications is indicated below:

1. Cross sectional study of HCV within a defined geographical region; prevalence and genotype distribution within high risk subpopulations

2. HCV – the silent epidemic. Assessing the magnitude of the undiagnosed HCV population from a cross-sectional study of high risk populations

9. References

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Research Plan Signature Page

AbbVie Ltd

Medical Research /Research Plan number

Study name – Study Title; Cross-sectional epidemiological study of HCV infection in a defined geographical region of Norway

Approved by:

_____ _____

(Insert Name) **Date:**

Medical/Scientific Lead

_____ _____

(Insert Name) **Date:**

Principal Researcher (if applicable)

_____ _____

(Insert Name) **Date:**

Affiliate & Operational Study Lead

_____ _____

(Insert Name) **Date:**

Affiliate Research International Medical Affairs

Study Governance

(only required for IMA multi-country studies).

9. Affiliate Agreement Page

AbbVie Ltd

Medical Research /Research Plan number

Study name – Study Title: Cross-sectional epidemiological study of HCV infection in a defined geographical region of Norway

Sponsor:

Name Medical Director: Steinar Thoresen

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Address: Martin Linges vei 25, Postboks 1, N-1330 Fornebu

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Local shipment address for DRFs/Questionnaires: (if applicable)

Name:

Address:

Address:

Country:

Phone:

Fax:

Requirements for non-interventional studies per local laws and regulations:

Competent Authority approval ☐

Competent Authority notification ☐

Competent Authority involvement not required ☐

Ethics Committee approval ☐X

Ethics Committee notification ☐

Ethics Committee involvement not required ☐

Written Patient Informed Consent required: ☐ No ☐X Yes

Regulatory requirements, other (if applicable): _____

Add Name

__Steinar Thoresen_____

Affiliate Medical Director name

_____ _____

Signature Date

10. Appendices

Participant Questionnaire