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PROTOCOL SIGNATURE SHEET

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Introduction

Chronic hepatitis C

It is estimated that the prevalence of hepatic C virus (HCV) among the Dutch population is 0.12%, implicating that there are over 19.000 HCV infected patients in the Netherlands. [1] Some 500 patients in the Netherlands die each year as a result of hepatitis B and C infection. [2]

Treatment

Until 2010, HCV treatment using (pegylated) interferon and ribavirin was associated with low efficacy and severe side-effects. As a result, only a selection of patients were treated and would easily be lost to follow-up. A recent study from Dutch hepatitis treatment centers estimated that up to one hundred chronic hepatitis C patients per center were lost to follow-up. [3][4]

In recent years HCV treatment has dramatically evolved due to the introduction of direct acting anti-virals (DAAs). New interferon-free all oral treatment regimes are now available with an efficacy as high as 95% and negligible side-effects. [5]

As of november 2015 a number of oral HCV targeting drugs have been allowed on the Dutch health care market and are fully reimbursed by the Dutch Healthcare Authorities for all HCV genotypes, independent of fibrosis stage. This recent development signals a new phase in the battle against hepatitis C epidemic and will lead to a significant improvement in prevention of HCV transmission, disease burden, and HCV-related complications.

National Plan

An initiative of experts from the hepatitis work field and the National Institute of Public Health and Environment (RIVM) has developed a strategy how to systematically move chronic HCV from endemic to an import disease. [6,7] This plan is supported by leading HCV experts in the Netherlands, representatives of the liver patient association (NLV) and biomedical industry. [1,8] One of the main elements of this strategy is focused on tracing chronic hepatitis C patients who are lost to follow-up, in addition to integration of multidisciplinary care in diagnosis and treatment.

Fibrosis

It is known that chronic hepatitis C patients have an increased risk of developing liver cirrhosis with associated complications such as the risk of hepatocellular carcinoma (HCC). Patients with advanced fibrosis and cirrhosis prior to treatment have a particularly high risk and these patients should be prioritized for treatment. [9]

Issue

We lack data with respect to the chronic hepatic C population that has been lost to follow-up over the last years. This information would be helpful to assist policymakers from other health care systems to judge whether an active track and trace policy would be beneficial and effective in their environment.

Aim

This project aims to map their disease course, stage of fibrosis and assess their risk of liver related complications in the population that is lost to follow-up.

Objectives

To coordinate active tracing of chronic hepatitis C patients lost to follow-up.

Primary objective:

- Establish liver fibrosis stage of the lost to follow-up population of chronic hepatitis C patients and comparison with our chronic hepatitis C population in regular care

Secondary objectives:

- Number and percentage (compared to total amount of ever diagnosed hepatitis C patients) of lost to follow-up patients
- Identification of reasons for lost to follow-up
- Provide a template for track and trace of lost to follow-up chronic hepatitis C patients that can be used and followed in other healthcare environments
- To compare patient and disease characteristics, comorbidities and co-medication between traced and regular care populations
- To establish an updated and professionalized registry that contains the complete chronic hepatitis C population. This registry may serve as a tool for clinical follow-up after treatment but will provide answers to important questions such as the interindividual rates of fibrosis regression and risk for hepatocellular carcinoma after viral clearance.

Hypotheses

We hypothesize that liver disease, expressed as fibrosis stage, is more advanced in the lost to follow-up population compared to patients under regular care, because we expect there is an overrepresentation of a number of disease specific characteristics in the lost to follow-up population such as: advanced liver disease (fibrosis), prior treatment failure (including discontinuation due to severe toxicity), difficult-to-treat genotype, and co-morbidities. Patients diagnosed > 10 years ago have a higher likelihood to be lost to follow-up due to limited treatment options in the past, and/or intolerance to interferon therapy.

Patient characteristics such as socio-economic status and physical and mental health issues (including substance abuse) may contribute to the risk to be lost to follow-up.

Study design

This is an prospective cohort study, which will start as a pilot study in the Radboudumc.

Population

In the pilot phase we aim to trace lost to follow-up chronic hepatitis C patients in the region Nijmegen. This so-called lost population consists of all patients, that in the past have been identified at the Radboudumc but who are currently lost to or have been withdrawn from follow-up. The time-span of

interest will be 2000-2015. We estimate that this project will retrace 100 lost patients through this search.
As a control group a cohort of patients with chronic hepatitis C under regular care will be used. This cohort consists of patients with hepatitis C treated with PEG-interferon, ribavirin and the first generation protease-inhibitors telaprevir and boceprevir between 2011-2015) and those who are or have been treated with new DAAs.

Inclusion criteria

-Ever diagnosed with hepatitis C, lost to follow-up

Exclusion criteria

-Younger than 18 years
-Unable to give informed consent

Primary outcome

- Fibrosis stage according to elastography (liver stiffness in kPa) and/or liverbiopsy (staging according to Metavir)

Secondary outcomes

- Number and percentage of (compared to total amount of ever diagnosed hepatitis C patients) of lost to follow-up patients
- Biomarkers of fibrosis: Enhanced Liver Fibrosis Test [10]
- Liver biochemistry prior treatment
- Liver related complications (hepatocellular carcinoma, cirrhosis, variceal bleeding)
- Patient characteristics and socio-economic status
- Reasons for loss to follow-up
- Disease characteristics (mode of infection, genotype, anti-HCV, PCR, viral co-infections (HBV, HIV), treatment attempts)
- Co-morbidities
- Co-medication
- Alcohol use and smoking behavior

Methods

Identification

- Identification of hepatitis C infected patients: a search of all HCV positive antibodies detected over the last 15 years (2000-2015) will be performed. This search will be conducted in participation with the medical microbiologists of the cooperating virology laboratories of the Radboudumc. The ‘RIVM handreiking’ identifies the medical microbiologist as a threating

physician (‘medebehandelaar’) and therefore allows a search through laboratory data to identify HCV infected patients, unless patients actively objected against exchange of medical data. [7]

- Identification of lost to follow-up patients: after all HCV positive patients have been identified the lost to follow-up patients have to be filtered out. Patients with a cleared acute infection or with effective treatment of a chronic hepatitis C infection can be excluded through chart review of the registries of the Radboudumc and other known regional certified hepatitis C treatment centres. This search is legitimized within the WGBO unless patients have actively objected against exchange of medical data. [7] Patients without any follow-up at the Radboudumc or another hepatitis centre are likely to be lost to follow-up and will be contacted. In the case of serology requested by the general practitioner we will contact the physician for clinical data on treatment and medical history of the patient.

Contact & Retrieval

- Before start of the project general practitioners will be informed about our initiative via a transmural newsletter.
- After identification, patients that are identified as lost to follow-up will be contacted: We will first ask permission from the general practitioner to contact these patients.
- The principal researchers will conduct contact with patients ourselves to achieve the highest patient response rate. A fulltime PhD student is appointed for coordination of this project.
- We will inform patients with an information and invitation letter in which we give information on the disease and on the new treatment options. We will invite patients at our outpatient clinic for a screening visit. In the invitation letter we make clear we want to give the patient more information by telephone and that we will call them in the week after the letter arrived. By adding the option of telephonic contact with the patients we hope to gain a higher response since we can explain more about new option treatments and answer to concerns of patients directly. Furthermore we will state clearly in the letter that the costs of the screening visit are not part of the national health insurance, therefore patients do not have to pay their own risk for this visit.

  We will emphasize the voluntary character of participation to the patients in this letter. Patients can reply with an answer form/by telephone in case they are not interested in participation. We will ask them to explain why they are not interested.

Screening visit

- The screening visit will be conducted at the Radboudumc.
- A hepatitis nurse can be reached by patients with questions regarding the screening visit.
- At the screening visit the patient will be given information about treatment options.

- A medical history of the patient will be taken, including co-medication, comorbidities, alcohol and tobacco use. Questionnaires concerning the reasons for loss to follow up and possible treatment difficulties in the past will be performed.
- To assess whether there is still a treatment indication blood samples will be drawn to assess HCV RNA, genotype, liver biochemistry and possible comorbidities. One tube of blood will be stored to assess viral resistance in case of treatment failure. Transient elastography (Fibroscan) and serum Fibrosis markers (ELF) will be performed to further assess fibrosis stage.

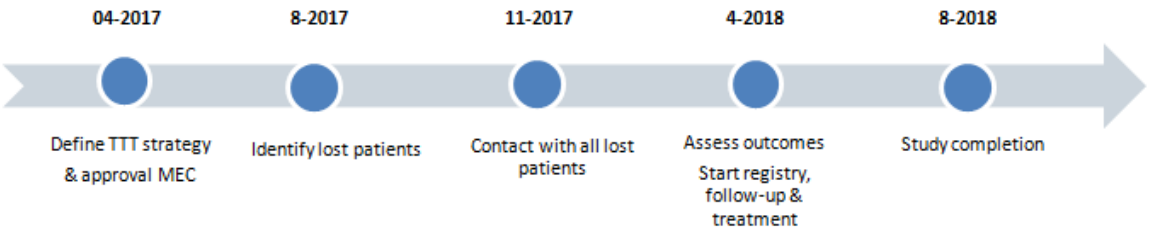
Treatment advice and follow-up

- After the screening visit patients will be called with the results of the tests performed and a patient-tailored advice concerning treatment indication and options.
- These results will also be sent to the general practitioner of the patient, who will be asked in case of a treatment indication to refer the patient to a consultant in the hospital for treatment. With this referral treatment falls under regular care. The patient will also receive this letter with the results.
- Depending on disease severity and preference of the patient the location of treatment will be decided. The ideal location of healthcare will be decided upon disease severity and preference of the patient. Patients will be followed in regular care according to current guidelines. [11, 12]

Outcome assessment

During the phases of identification, contact, retrieval and screening of lost to follow-up patients the data concerning our primary and secondary objectives will be collected. Disease severity of the lost to follow-up group will be compared with a retrospective cohort of hepatitis C patients under regular care and treated in the Radboudumc.

Figure 1. Timeline study duration



Withdrawal of individual subjects

Patients can at any moment in the study, without justification, decide to stop their participation.

Safety reporting

Not applicable, since it does not concern an interventional study.

Statistical Methods

Descriptive analyses will be performed for baseline data (mean ±SD, median, interquartile range). The primary outcome difference in fibrosis stage will be tested between the lost chronic hepatitis C group and control group. To compare different characteristics of the groups either a chi-square test, t-test or Mann-Whitney U test will be used, according to the distribution of variables. Differences between groups will be considered significant at *P* values <0.05. Analyses will be performed using the statistical package SPSS, version 22.0 (SPSS Inc. Chicago, IL, USA).

Power/Sample Size

Not applicable.

Ethical considerations

Ethical approval from the CMO Arnhem-Nijmegen will be obtained to contact patients. Patients will be asked informed consent for registration of their anonymized data in the Castor database. The Code of Conduct for the Use of Data in Health Research will be taken into account. [13]

Recruitment and consent

For recruitment procedures see methods of retrieval section.

Informed consent will be obtained of all participants before the screening event. See the informed consent form, attached to the patient information file, for which specific procedures we obtain consent.

Benefits and risks assessment

As a result of participation in this study the lost to follow-up population could benefit from re-entry in to the regular health care system and if indicated and wanted by the patient treatment of their chronic hepatitis C. The minimal risks of this study (inconveniences of blood withdrawal, possibility of unexpected medical findings) do not outweigh this benefit.

Compensation for injury

Since this concerns an observational study, with only a single blood withdrawal as invasive measurement and no interventions, we deem it not necessary to conclude a specific participants insurance (proefpersonenverzekering). We request the CMO dispensation for this insurance. The Radboudumc has a liability insurance applicable to all study participants.

Incentives

There are no incentives for participants. The measurements during the screening event will be financied from a fund we received from MSD. Therefore these costs will not be accounted to the health insurance of participants or withdrawn from their own risk (eigen risico zorgverzekering).

Data management

Data will be encrypted, and every patient receives an unique code, based on chronological availability of the data. A validated data management program, termed CastorEDC will be used for data storage. This is a web-based data management system with a high security profile through log-in and data-access authorizations. Data-entry is secured with an audit trail. This database can be used as a registry for follow-up (research).

Storage of residual material

For all patients that participate in the clinical screening one serum tube will be stored for viral resistance measurement in case of treatment failure. If this material will not be used for clinical purposes we can use this residual material for future research. We will request a separate approval for use of this residual material. Material will be stored with the same patient encrypment used for clinical data, at the departments biobank.

Monitoring

We stratify the risk, based on the NFU risk classification in human research, as negligible. This is an observational study with only a single blood withdrawal and not performed in vulnerable patient category. Therefore no on-site monitoring will be necessary. [14]

Annual progress report

The investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial and amendments.

End report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient’s last visit. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

Publication policy

Several scientific manuscripts will be published with the results of this study. For policies regarding ownership of data and publications see research contract, page 11.

Disclosure of support
See research contract, page 11.

Future perspectives

If implementation of the track, trace and treat strategy is successful, expansion to the region will take place in a second phase, with inclusion of two more certified hepatitis treatment centers: Canisius Wilhelmina Hospital in Nijmegen and Jeroen Bosch Hospital in Den Bosch. Eventually our goal is to implement a nation-wide network in which all hepatitis C patients in the Netherlands will be offered treatment.

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