Hôpitaux Universitaires de Genève

Département des Spécialités de Médecine

Service de Gastroentérologie et d'Hépatologie

Swiss Hepatitis C Cohort Study: CCER 00-28

Clinical Study Protocol

Sponsor-Investigator: Pr. Francesco Negro

Protocol Version and Date: Version 2 – 15.04.2015

CONFIDENTIAL

Signature Page(s)

Study number 00-28

Study Title Swiss Hepatitis C Cohort Study

The Sponsor-Investigator and trial statistician have approved the protocol **version 2 - 15.04.2015**, and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Sponsor-Investigator:

Prof. Francesco Negro

Place/Date Signature

Principal Co-Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

Study site:

Principal Co-Investigator:

Place/Date Signature

**Note:* In multicentre studies, this page must be individually signed by all participating Local Principal Investigators.

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Sponsor-Investigator	Prof. Francesco Negro
Study Title:	Swiss Hepatitis C Cohort Study
Protocol Version and Date:	Version 2 - 15.04.2015
Trial registration:	Registered at the "Swiss platform of medical registries" (FMH website): http://www.fmh.ch/fr/asqm/_service/plateforme_suisse_des_registre.cfm
Background and Rationale:	The Swiss Hepatitis C Cohort Study (SCCS), established in 2000 is a systematic longitudinal study enrolling subjects with positive serology for HCV in Switzerland. It is a collaboration of all Swiss University Hospital outpatient clinics, two large cantonal hospitals, all with affiliated laboratories, and with affiliated smaller hospitals and private physicians caring for HCV patients. The major goal is to provide a platform for carrying out scientific research projects in the field of hepatitis C.
Inclusion / Exclusion criteria:	Anti-HCV positive patients aged more than 18 years will be enrolled throughout Switzerland, at both university hospitals and other participating centers
Measurements and procedures:	Visits: Enrolment visit and one follow-up visit at least once a year, except in patients undergoing antiviral treatment, where additional visits are planned Whole blood collected for biobanking at least once a year Optionally, if available and collected from normal clinical procedures: liver fragments obtained at the time of biopsies carried out for diagnostic purposes
Number of Participants with Rationale:	Number of subjects projected for the entire study (all sites combined): **7,000** (corresponding to 10% of the estimated global HCV-infected population residing in Switzerland)
Study Duration:	Estimated duration for the main investigational plan (e.g. from start of screening of first participant to last participant processed and finishing the study): **unlimited duration**

Investigators:	Prof Francesco Negro Services de Gastroentérologie et d'hépatologie et de Pathologie clinique Hôpitaux Universitaires de Genève 4, rue Gabrielle-Perret-Gentil 1211 Genève 14 Phone +41-22-3729355, e-mail Francesco.Negro@hcuge.ch Prof. Andreas Cerny Epatocentro Ticino Via Soldino 5 6900 Lugano Phone +41-91-9608503, e-mail andreas.cerny@bluewin.ch Prof. Jean-François Dufour Universitätsklinik für Viszerale Chirurgie und Medizin Inselspital Freiburgstrasse 3010 Bern Phone +41-31-6322111, e-mail jf.dufour@ikp.unibe.ch Prof. Markus Heim Abteilung für Gastroenterologie und Hepatologie Universitätsspital Petersgraben 4 4031 Basel Phone +41-61-2653362, e-mail markus.heim@unibas.ch Prof. Raffaele Malinverni Département de Médecine Hôpital Nechâtelois, Site Pourtalès Rue de la Maladière 45 2000 Neuchâtel Phone +41-32-7133589, e-mail Raffaele.Malinverni@ne.ch Prof. Darius Moradpour Service de Gastroentérologie et d'Hépatologie Centre Hospitalier Universitaire Vaudois Rue du Bugnon 44 1011 Lausanne Phone +41-21-3144714, e-mail Darius.Moradpour@chuv.ch Prof. Beat Müllhaupt Gastroenterologie Abteilung Universitätsspital Frauenklinikstrasse 10 8091 Zürich Phone +41-44-2552553, e-mail beat.muellhaupt@usz.ch Dr David Semela Klinik für Gastroenterologie und Hepatologie Kantonsspital St. Gallen Rorschacherstrasse 95 9007 St.Gallen +41-71-4941216, e-mail David.Semela@kssg.ch

Study Centres:	Service de Gastroentérologie et d'hépatologie Hôpitaux Universitaires de Genève 4, rue Gabrielle-Perret-Gentil 1211 Genève 14 Epatocentro Ticino Via Soldino 5 6900 Lugano Universitätsklinik für Viszerale Chirurgie und Medizin Inselspital Freiburgstrasse 3010 Bern Abteilung für Gastroenterologie und Hepatologie Universitätsspital Petersgraben 4 4031 Basel Département de Médecine Hôpital Nechâtelois, Site Pourtalès Rue de la Maladière 45 2000 Neuchâtel Service de Gastroentérologie et d'Hépatologie Centre Hospitalier Universitaire Vaudois Rue du Bugnon 44 1011 Lausanne Gastroenterologie Abteilung Universitätsspital Frauenklinikstrasse 10 8091 Zürich Bereich Gastroenterologie und Hepatologie Kantonsspital Rorschacherstrasse 95 9007 St.Gallen
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP as well as all national legal and regulatory requirements.

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STUDY SUMMARY IN LOCAL LANGUAGE

The lay summary in the local language may be provided here (French)

ABBREVIATIONS

AE	Adverse Event
CA	Competent Authority (e.g. Swissmedic)
CEC	Competent Ethics Committee
CRF	Case Report Form
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
CTU	Clinical Trial Unit
FOPH	Federal Office of Public Health
FSO	Federal Staistical Office
GCP	Good Clinical Practice
HCV	Hepatitis C Virus
HRA	Federal Act on Research involving Human Beings
ICF	Informed Consent Form
IFN	Interferon
ISPM	Institute of Social and Preventive Medicine
LPTh	Loi sur les produits thérapeutiques
LRH	Loi fédérale relative à la recherche sur l'être humain
LTFU	Lost to Follow-Up
OClin	Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain *(in German : KlinV, in English : ClinO)*
PI	Principal Investigator
SCCS	Swiss Hepatitis C Cohort Study
SDV	Source Data Verification
SNC	Swiss National Cohort
SOP	Standard Operating Procedure
SSN	Social Security Number (also referred to as, in local language, AVS [Assurance Vieillesse et Survivants] or AHV [Alters- und Hinterlassenenversicherung])
SVR	Sustained Virological Response
TMF	Trial Master File

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Study Periods	Enrolment visit	Follow-up visit				
Visit	1	2	3	4	…	….
Time (month)	0	12	24	36	…	….
Patient Information and Informed Consent	x					
Demographics	x					
Medical History	x	x	x	x	x	x
In- /Exclusion Criteria	x					
Physical Examination	x	x	x	x	x	x
Vital Signs	x	x	x	x	x	x
Blood tests	X	X	X	X	X	X
Antiviral treatment history	X	X	X	X	X	X
Blood collection for storage (~20 ml)	x	x	x	x	x	x

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1. STUDY ADMINISTRATIVE STRUCTURE

1.2 Sponsor

The SCCS is sponsored by Prof. Francesco Negro, Service de Gastroentérologie et d'hépatologie et de Pathologie clinique, Hôpitaux Universitaires de Genève, rue Gabrielle-Perret-Gentil 4, 1211 Genève 14), current Chairman of the Swiss Hepatitis C Cohort Study Foundation.

This study is a sort of register and the sponsor has no other role than making sure that the appropriate support for the correct execution of the study is available at the study sites. The study design, the collection, management, analysis, and interpretation of data and the writing of the reports, including scientific manuscripts, presentations at scientific events and any other pertaining reports with any media support are responsibility of the SCCS investigators.

1.3 Principal Investigators

Each study site is led by a Principal (Co)-Investigator, who is in charge of all site-related medical decisions. They may delegate medical decisions to Sub-Investigators working at the same or different departments of the same institution, or at neighbouring (satellite) institutions and affiliated at the main study center. The **Principal (Co)-Investigators** are:

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1.4 Statistician

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1.5 Laboratory

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Other accredited laboratories that may provide data to be entered in the patients' e-CRF are:

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Covance Inc.
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1.6 Monitoring institution

No monitoring is foreseen for this of study.

1.7 Any other relevant Committee, Person, Organisation, Institution

Data center and data management:

Pascal Benkert and Patrick Simon

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1.8 Study registration

Registered at the “Swiss platform of medical registries” (FMH website):

http://www.fmh.ch/fr/asqm/_service/plateforme_suisse_des_registre.cfm

The study website is also available at http://www.swisshcv.ch/

1.9 Ethical Conduct of the Study

The responsible investigator at each site ensures that approval from an appropriately constituted Competent Ethics Committee (CEC) is sought for the clinical study. No changes are made to the protocol without prior Sponsor and CEC approval.

The study is carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the Swiss Law and Swiss regulatory authority’s requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study end in agreement with local requirements.

1.10 Declaration of interest

There are no conflicts of interest (independence, intellectual, financial, proprietary etc) to be mentioned.

1.11 Patient Information and Informed Consent

The investigators will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The subject must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All subject for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. The patient information sheet and the consent form have been submitted to

the CEC to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the subject is submitted to any study procedure.

The subject should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

1.12 Participant privacy and confidentiality

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality is ensured by utilising subject identification code numbers when personal data are entered in the e-CRF. Anonymity of the participants is guaranteed when presenting the data at scientific meetings or publishing them in scientific journals. Some samples can be anonymised (no name and not code) before sending to other laboratories and institutions.

For data verification purposes, authorised representatives of the Sponsor, a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

2. BACKGROUND AND RATIONALE

HCV is a human pathogen affecting ~2.4% of the global population (Mohd Hanafiah et al, 2013), and a major cause of both hepatic and extrahepatic morbidity and mortality worldwide (Lee et al, 2012), resulting into an estimated ~350,000 deaths annually (Wiersma, 2011). HCV causes acute and chronic hepatitis, the latter progressing – over years to decades – to cirrhosis and hepatocellular carcinoma (HCC). Decompensated HCV-related cirrhosis is the leading indication to liver transplantation in most developed countries. In Western Europe, the proportion of cirrhosis and HCC cases attributable to HCV is 38% and 44%, respectively (Perz et al, 2006). Although HCC is the sixth most common neoplasm worldwide, its very poor prognosis makes it the third leading cause of cancer related mortality, responsible for ~600,000 deaths annually. Although globally only 10–25% of HCC cases are thought to be associated with HCV infection, this proportion can be as high as 60% in Western countries, due to the relatively lower incidence of hepatitis B virus (HBV)-associated HCC as compared to Asia and Africa (Perz et al, 2006; Mittal and El-Serag, 2013). In addition to liver-related complications, HCV is also associated with a significant increase in extrahepatic diseases and mortality, mostly deriving from type 2 diabetes, cardiovascular and renal complications (Lee et al, 2012). The relationship between HCV infection and glucose and lipid metabolic alterations – leading to steatosis, insulin resistance and chronic systemic inflammatory and prothrombotic states – has been known for years and is reviewed elsewhere (Uthman and Gharavi, 2002; Bugianesi et al, 2012).

Despite scientific advances in the field of the virology and the pathogenesis of hepatitis C and the development of new antiviral strategies that may culminate in the introduction of all-oral, interferon-α (IFN-α)-free regimens in 2015-2016 for all patients, the HCV epidemic continues to advance and take its toll, as reflected by the increased morbidity and mortality due to HCV. Modelling studies have shown that the prevalence of HCV-related cirrhosis will increase to 37% of all hepatitis C cases by 2020, and 45% of all cases by 2030 (Davis et al, 2010). In the US, the HCV-associated mortality has surpassed the mortality due to HIV in 2007: despite this, HCV obtains 30 times less research funding than HIV (Edlin, 2011; Ly et al, 2012). Regrettably, HCV-related mortality in Switzerland is estimated to increase further until 2030 (Mullhaupt et al, in press). This situation is due to several factors. First, more than half of the persons living with HCV are undiagnosed, due to the asymptomatic course of the infection, to a general lack of awareness about the disease and its consequences and to the intrinsic limitations of current screening policies (Rein et al, 2012). Thus, many patients are identified at the cirrhotic stage or at an older age, i.e. when significant comorbidities have set in, rendering antiviral therapy more complex and potentially ineffective, if not harmful. Second, most new infections occur in people who inject illicit drugs, where prevention strategies have met with limited success, treatment is difficult and reinfection is frequent. Third, access to currently available treatments, is still limited by their high prices, which has imposed severe restrictions to their use. Furthermore, a proportion of cirrhotic patients, even in case of treatment-induced viral eradication, may still develop HCC (Aleman et al, 2013). Finally, although liver transplantation may be curative of decompensated cirrhosis, a substantial proportion of patients – between 15 and 50%, depending on the donor rates, disease prevalence and other factors – die on the waiting list due to lack of suitable organ donors. When successfully transplanted, patients develop recurrent HCV infection which can rapidly progress to graft

failure. Thus, more aggressive screening strategies have been suggested, such as the birth cohort screening recently proposed by the US CDC, aiming at identifying patients at early disease stages, allowing safer and more effective management before cirrhosis develops: this approach was shown to be cost-effective (Rein et al, 2012) and may prevent 82,000 HCV-related deaths in the US alone. An extension of the criteria for HCV screening has been recently proposed also in Switzerland by a panel of specialists involved in different sectors related to HCV management and policy-making (Fretz et al, 2013).

Nationwide cohort studies on HCV-infected persons have been set up in the past ten years in many Western countries, such as the UK (The Trent HCV Cohort), France (the several cohorts supported by ANRS including the more recent HepaTher, which will include 15,000 hepatitis patients), and Germany (the Hep-Net Consortium). Based also on the success of another Swiss cohort study, the Swiss HIV Cohort Study (SHCS), the SCCS was established in 2000 as a prospective cohort of anti-HCV-positive persons seen at 8 major hospital across Switzerland, i.e. the 5 University teaching hospitals (Basel, Bern, Geneva, Lausanne, Zurich) plus 3 major referral regional hospitals (Hôpital Pourtalès in Neuchatel, Kantonsspital St. Gallen and Clinica Moncucco in Lugano), covering most regions of the country. The SCCS population consists of adults with a confirmed anti-HCV-positive assay. The SCCS population is representative of the general HCV-infected population across the country, as shown by the study conducted in 2007 in collaboration with the Institute of Social and Preventive Medicine of the University of Berne, and the Swiss Federal Office of Public Health (FOPH) (Prasad et al, 2007). This analysis showed that the SCCS population is similar to the Swiss national surveillance data in terms of age at diagnosis, sex, nationality and the most frequently reported risk factors for HCV. Thus, the main strength of the SCCS lies in the fact that it should provide generalizable results on the progression of hepatitis C and allow conducting nested studies, e.g. investigating new treatments and supplementing epidemiological data collected by the mandatory national surveillance system at the FOPH.

The SCCS patient data (and samples) have provided the basis for numerous scientific publications, such as the independent discovery of *IL28B*/*IFNL3* genetic polymorphisms affecting HCV clearance, both spontaneous and treatment-induced (Rauch et al, 2010). Follow-up articles have clarified the role of these same polymorphisms in affecting other HCV-associated phenotypes such as steatosis (Cai et al, 2010), liver inflammation and fibrosis (Bochud et al, 2012), and led also to the identification of a novel polymorphism that is associated with *IL28B* expression and that may explain the mechanism of HCV clearance (Bibert et al, 2013; Terczyńska-Dyla et al, 2014). Genetic markers have been thoroughly investigated also as far as it concerns predictors of HCC development, in close collaborations with patient cohorts from Germany and Japan, and led to publications on SNPs in *CYP27B1* and *HCP5* (Lange et al, 2013a; Lange et al, 2013b). In more general terms, the identification of clinical, virological and genetic markers of liver disease progression has been the focus of several other studies (Muzzi et al, 2005; Bochud et al, 2009), including the first genome-wide association (GWA) study ever performed on host genetic variants associated with liver fibrosis progression, in collaboration with a French ANRS cohort (Patin et al, 2012). All of the above observations will pave the way for more mechanistic studies on the pathogenesis of HCV infection. It is important to mention that the data found in the SCCS database are available to other investigators (including cohort study groups) in the setting of collaborative projects.

Therefore, the primary purpose of the SCCS is to serve as a framework for projects addressing specific issues concerning the pathogenesis and management of HCV.

2.1 Risks / Benefits

This cohort study does not foresee specific interventions (neither diagnostic nor therapeutic) that may affect patients' safety. On the other hand, patients enrolled in the SCCS may profit indirectly of their participation in the study, because they could be the first ones to benefit of the application of the results of the most relevant studies conducted with the data and samples collected within the SCCS.

2.2 Justification of choice of study population

The patients enrolled represent the typical HCV-infected population, since no subgroups of HCV-infected persons (except minors) are excluded. The study does not involve the enrolment of vulnerable patients' populations.

3. STUDY OBJECTIVES

The primary purpose of the SCCS is to serve as a framework for projects addressing specific issues concerning the pathogenesis and management of HCV.

4. STUDY OUTCOMES

The study will assess the most relevant scientific questions related to the epidemiology, pathogenesis, natural course and response to therapy of HCV infection in adults. The issues to be covered include the determinants facilitating infection with HCV, the factors associated with spontaneous clearance at the time of primary HCV infection, the factors influencing the progression of hepatitis C to advanced stages of liver disease – including primary liver cancer – and affecting mortality, those influencing the response (or lack thereof) to antivirals; the interactions with other cofactors of pathogenesis, including environmental and behavioral variables; the safety and long-term efficacy of antiviral therapy; the relevance of extrahepatic manifestations in HCV infection, and how treatment may affect them.

The collection of a vast and representative sample of HCV infected persons in Switzerland may also provide the framework for public health assessments and interventions, and cost-utility analyses of specific treatments or diagnostic procedures and algorithms.

5. STUDY DESIGN

5.1 General study design and justification of design

Persons fulfilling the eligibility criteria are assigned a 5-digit code at enrolment. Thus, all data and material are coded. The list of codes is kept by each single participating investigator. Duplicate enrolments are ruled out by identifying each patient (apart from the five-digit code) with his/her date of birth, sex and height.

At enrolment and at each follow-up visit, performed annually, data on demographic characteristics, social and educational background, occupation, risk factors for HCV infection, history of alcohol drinking, major events of medical interest (e.g. pregnancy, use of illicit drugs, imprisonment, transplantation, diabetes and others) and prior antiviral therapy, are recorded according to standardized questionnaires. In addition, a full panel of blood test results is collected, including serological assays for HCV, HBV, HDV, and HIV. Since April 22, 2013, data are entered in a web-based system (e-CRF) for data collection (SecuTrial), managed by the Clinical Trial Unit of the University Hospital of Basel. This collaboration is deemed crucial to ensure the standardization of the data collection and quality and consistency of the database. In particular, safety data will be collected according to international standards in order to make databases comparable among different cohort studies. The detailed modalities for data collection are described in the handbook (SOP for data collection, see Annexes).In addition to the clinical data, the SCCS collects at every visit a blood sample, stored in the form of plasma and peripheral blood mononuclear cells at repositories located at the participating centers. Storage follows standard biobanking criteria of quality. Cells are also the source of DNA for genetic studies. A Standard Operating Procedure for evaluating the feasibility of a study and to obtain data and biosamples from the Basel CTU is attached (see Annexes, SOP for biosample handling) and available on the SCCS website. As said above, any investigator (or group of investigators, including other Cohort Study Groups) can access the SCCS data for research projects, pending the approval – based on feasibility and scientific merits – of the SCCS Scientific Committee, following the procedures outlined in the SCCS website.

6. STUDY POPULATION

6.1 Eligibility criteria

To be enrolled in the SCCS, patients must fulfill the following criteria:

- To test positive for serum anti-HCV antibodies by a third generation EIA;
- To be ≥18 years old;

- To be resident in Switzerland;
- To accept to be followed at one of the study centers;
- To have signed the SCCS informed consent form.

6.2 Recruitment and screening

Patients are enrolled at one of the study centers by one of the Principal (Co)-Investigators or one of the Sub-Investigators or one of his/her delegates provided that the latter ones performed a training in Good Clinical Practice as required by the law. In principle, all persons fulfilling the eligibility criteria described in section 6.1 and consecutively seen by the above mentioned investigators and/or their delegates can be enrolled without any sort of selection leading to a study population enrolment bias.

Patients are anonymized by assigning to each of them a unique five-digit code. The list of codes is kept by each single participating investigator. Duplicate enrolments are ruled out by identifying each patient (apart from the five-digit code) with his/her date of birth, sex and height.

Participants are not given any payment or any sort of compensation for medical and other costs incurred during the time of participation to the SCCS. Patients undergo all routine examinations – including outpatient and inpatient consultations, blood tests, ultrasound examination of the abdomen, liver biopsy, non-invasive assessments of liver fibrosis – as required by the usual diagnostic and therapeutic management of patients with HCV infection according to the state-of-the-art knowledge in the field: thus, the cost of these medical procedures are paid for each patient's medical insurance. No additional interventions – diagnostic or therapeutic – are required in association with the participation to the SCCS. Patients are requested only to allow the collection of their blood in the total amount of ~20 ml once a year, but the material and the procedures associated with this are entirely free of charge.

6.3 Criteria for withdrawal / discontinuation of participants

6.3.1 Withdrawal of patients from the study

Patients are withdrawn from the study in the following cases:

- The patient has died;
- The patient has stably emigrated to another country;
- The patient has explicitly declared his/her unwillingness to continue (opt-out);
- The patient has agreed with the investigator that it is more convenient to be followed by his/her general practitioner or other specialist who is not a SCCS investigator, especially when (i) he/she is SVR after therapy; (ii) he/she has moved to a new Swiss address significantly afar from the study center. In such cases, the patient is withdrawn from the study, but the investigator assigns the patient to the category "In care at a non-SCCS center". The name of the new treating physician should be recorded by the local investigator.
- The patient has not responded by any means to at least two written invitations, after no follow-up visits have been performed 24 months from the latest follow-up visit: in this case, the patient must be stopped according to the instructions in the handbook (see SOP for data collection, Annexes). However, this must be a last resort procedure, since all efforts should be made to contact patients who fail to show at the annual visit, also to evaluate in due time the patients' eligibility to the novel, potent and safe antiviral treatments that may become available in the future.
- The patient has changed address without informing the study site.

In the above circumstances, the investigator of his-her delegates fills the appropriate form designed as Stop/Re-Entry in the electronic database (see SOP for data collection, Annexes).

6.3.2 Re-entry after withdrawal

Patients can re-enter the study at any time and independently of the reason why they had decided to leave the study. If patients had left the study because of unwillingness to continue, a new consent form has to be signed, with a new date. This is reported and can be checked in the e-CRF. Data collected and available between the date of discontinuation and re-entry (including those regarding antiviral therapy) should be entered in the e-CRF (see SOP for data collection, Annexes).

6.3.3 Change of study center

Patients who move around Switzerland and are followed at a new study center do not change their subject identification code numbers within the study. The right to access the respective e-CRF page is reassigned by the Basel University CTU to the new center after written agreement between the former and the new study center. The detailed modalities of this procedure are reported in the SOP for data collection (Annexes).

6.4 Data Collection and Tracking of Lost to Follow-Up (LTFU) participants

Patients who have not been seen at any of the study centers for at least 24 months and have not responded to at least two written invitations are withdrawn from the study (section 6.3.2) and are in principle lost to follow-up (LTFU). However, since they have not explicitly declared their unwillingness to continue the study, data concerning their health status (in particular regarding mortality and cause of death, if applicable) is still collected for statistical and epidemiological purposes. A specific statement is included in the ICF whereby the patients accept this procedure at the act of enrolment.

This paragraph describes in detail the procedure to track the LTFU's vital status and the cause of death, whenever applicable.

First, the investigator checks all internal information sources of his/her study site. Deaths are recorded in some cantons in public databases (e.g. Geneva). If no data is retrieved in this way, there are two additional sources for assessing the vital status of participants: (i) the Mortality registry of the Swiss Federal Statistical Office (FSO) and (ii) the person registry of each municipality. In 2008, a new social security number (SSN) was introduced and, since 2010, this number is included in the person registry of the FSO and on the individual health insurance card. The health insurance card is used at each hospital for invoicing patients. To track the LTFU participants, two scenarios are set up at each participating clinic, depending on the date when patients were seen for the last time:

1. If the date when the patient was seen for the last time falls before 2010, the LFTU person will be tracked by calling the municipality of the last known address.
2. If the date when the patient was seen for the last time is in 2010 or later (and therefore most likely the patient's new SSN is available at the study center), the LTFU person will be tracked down by using the address database and the mortality registry of the FSO.

In the first scenario, the name, first name, date of birth and the last known address will be sent to the municipality of the last known address with the request to a) confirm the address (i.e. if the patient is still there), b) to send the new address (or at least the new municipality of residence, or c) to send the date of death. If the patient has moved, the same request will be sent to the new municipality, until the current address or date of death is available. Since it is expected that some municipalities may be reluctant to provide the requested information, the letter of approval of this procedure by the local CEC will be sent as attachment. This procedure will provide the date of death of the deceased persons, but not the causes of death. The causes of death will be retrieved by linking these records anonymously with the Swiss National Cohort (SNC) at the Institute of Social and Preventive Medicine (ISPM) in Berne, using date of birth, date of death, gender, nationality and municipality. A project specific contract based on a SNC form will be negotiated between the SCCS, the SNC and the FSO for linking the above mentioned data.

In the second scenario, the SSNs (together with name, sex, date of birth and nationality) will be sent to the FSO by each investigator, i.e. the person who is responsible for coding each patient, or one of his/her delegates. The FSO has, since 2010, the SSN, name and address, which they receive from each municipality in Switzerland, stored (mandatory) in their population database. The FSO will use this information to identify persons who are registered in the mortality registry. This will provide the date of death and causes of death, whenever applicable. This procedure can only be applied for patients LTFU after January 1st, 2010, as the new Swiss SSN wasn't available at the FSO before. A project specific contract based on a FSO form will be negotiated between the SCCS and the SFO for linking the above mentioned data.

6.5 Trial specific preventive measures

There are no restrictions of prohibitions for the study participants concerning any treatment, unless this is medically indicated.

6.6 Adverse events

Whenever adverse events result in changes of the antiviral treatment dosage and schedule, this is

reported in the relevant therapy section of the e-CRF.

7. SAFETY

Not applicable to this study.

8. BIO-SAMPLING

At each routine study visit, performed once a year, whole blood is collected for storage, on top of what is routinely done for diagnostic assays. The amount of blood is established as follows:

1. **Plasma**: one 6 ml EDTA tube to prepare 3 aliquots of plasma (each of at least 0.9 ml);

2. **Cell pellets for host DNA storage** (3 aliquots per visit, for at least 3 visits, then stop). Centres may use one of two procedures (for technical details see SOP for blood sample collection, Annexes), at their own choice:
   - Two 4 ml CPT tubes (Cell Preparation Tube, Becton Dickinson, No. 362760), or:
   - Two 6 ml EDTA tubes.

When patients receive antiviral therapy (but only in this case), different (i.e additional) time points are foreseen at baseline pre-treatment), week 2, week 4, week 12, week 24 [if applicable], end of treatment [if not 12 or 24 weeks], and 12 weeks after the end of treatment. At the time of these treatment-related visits, only plasma can be collected. This collection is optional and consists in one 6 ml EDTA tube for 3 aliquots of plasma (of 0.9 ml each).

Liver biopsies are not required for the study. However, it is possible to collect snap frozen (preferably in liquid nitrogen) fragments of liver tissue taken at the time of biopsy done for diagnostic purposes (or at the time of surgery in case of liver transplantation or other surgical procedures), provided that the amount of material stored for further research does not interfere with the appropriate diagnostic procedure.

8.1 Determination of Sample Size

The study plans to enroll a total of 7,000 anti-HCV-positive persons. This corresponds to the 10% of the estimated total HCV-infected population in Switzerland. It is assumed that this size – even allowing a 30% attrition rate – should allow analysing most patients' subgroups with sufficient detail.

8.2 Handling of missing data and drop-outs

Despite of a carefully planned and conducted study, some data will be missing and persons will drop out. Missing data is a potential source of bias, but there is no universal best approach for handling it. In case of substantial percentage of missing data, multiple imputation is a method which is practical and widely used. After applying methods to handle missing values, sensitivity analysis will be done, a) comparing different strategies and b) comparing processed data analysis with complete case analysis. Drop-outs will not be replaced but adjusted for using respective statistical methods, e.g. Cox regression for longitudinal and survival data, which handles censored and truncated data.

9. QUALITY ASSURANCE AND CONTROL

Appropriate Standard Operating Procedures for collecting data and clinical samples are available in French and German (see Annexes). The Study Coordinator is conducting regular site visits to address management issues with the local study personnel.

9.1 Data handling and record keeping / archiving

9.1.1 Case Report Forms

Data are collected in the form of electronic Case Report Forms (e-CRF) using the electronic data capture system secuTrial. Each enrolled study participant has a dedicated e-CRF page. CRFs are

kept current to reflect subject status at each phase during the course of study. Participants are not identified in the CRF by name or initials and birth date: rather, an appropriate subject identification code number is used, and consist of five alphanumeric digits. The first digit identifies the study center: 1 = Zurich; 2 = Basel; 3 = Bern; 4 = Geneva; 5 = Lausanne; 6 = Lugano; 7 = St. Gallen. Patients enrolled at the study site of Neuchatel are identified by 55 being the two initial digits of their codes.

9.1.2 Specification of source documents

Source data are available at each study site to document the existence of the study participants. Source data include the original documents relating to the study, as well as the medical treatment and medical history of each participant.

Source documents found at each study site in paper and/or electronic form include the patients' demographic data, visit dates, Informed Consent Forms, data on blood tests, liver biopsy and antiviral treatment, treatment-associated AEs and results of other relevant examinations. Data that are directly recorded in the e-CRF, which is considered – as a consequence – source data include the subject's nationality, ethnicity, geographical origin, the highest completed educational degree, the present occupational situation, the risk factors for HCV acquisition, the alcohol drinking habits, and data on pregnancy/delivery, treatment for depression or other psychiatric disorders, imprisonment, drug substitution programs, use of illicit drugs, organ transplantation, diabetes, and detailed information on prior or current antiviral therapy.

9.2 Data management

9.2.1 Data Management System

The clinical trial data will be collected in the electronic data capture (EDC) system named secuTrial (interActive Systems GmbH (iAS), Berlin). The website of the cohort study is available under https://secutrial.uhbs.ch/apps/WebObjects/ST21-productive-DataCapture.woa/wa/choose?customer=SCCS.

The EDC system runs on a server maintained by the IT-department of the University Hospital Basel. The e-CRF is implemented (set-up and adjusted) by the datamanagement group at the Clinical Trial Unit (CTU) at the University Hospital Basel.

9.2.2 Data security, access and back-up

Password protection ensures that only authorized persons can enter the system to view, add or edit data according to their permissions. User administration and user training is performed by the CTU according to predefined processes.

An audit trail system maintains a record of initial entries and changes (reasons for changes, time and date of changes, user identification of entry and changes).

Back-up of secuTrial study data is performed according to the processes of the IT-department of the University Hospital Basel.

9.2.3 Analysis and archiving

Data extraction and analysis for scientific projects is performed by the CTU data center given the project has been approved by the scientific board of the cohort.

After a possible end of the study, data is exported by the CTU according to internally defined processes and transferred to the investigator. Data will be archived by the investigator.

9.2.4 Electronic and central data validation

Data verification is done by the EDC system itself (e.g. data format checks) and by rule-based checks implemented for a variety of fields (e.g range checks, data checks etc.). In addition, central data validation is performed by the CTU data center upon request. Identified inconsistencies are communicated and solved by means of queries within the EDC system.

9.3 Monitoring

No monitoring is foreseen for this study.

9.4 Confidentiality, Data Protection

All data will be coded: subject data will be identified by a unique study number containing no personally identifiable information (PII) in the e-CRF. A separate confidential file containing PII will be stored in a secured (locked) location in accordance with data protection requirements. Study investigators have access to the records. Moreover, direct access to source documents and records will be permitted to the EC and regulatory authorities for purposes of audits and inspections and to the sponsor for monitoring activities, if it will be the case.

9.5 Storage of biological material and related health data

Biological samples are stored indefinitely, unless otherwise requested by each study subject. Regarding the Biobank storage, samples or genetic data are only stored with the participants consent.

10. PUBLICATION AND DISSEMINATION POLICY

The results of studies carried out using data and clinical samples collected within the setting of the SCCS will form the object of scientific publications (presentations at scientific conferences, manuscripts to be submitted to journals with or without editorial policy). Descriptive analyses on selected features of patients enrolled in the SCCS may be the object of reports on the SCCS website available at the URL http://www.swisshcv.ch/ or to be shared with third parties. The access to the SCCS resources is restricted and subjected to approval – based on scientfiic merit and feasibility – by the SCCS Scientific Committee.

10.1 Composition of the Scientific Committee

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10.1 Guidelines for scientific nested projects

The SCCS welcomes all research in the form of Scientific Nested Projects (SNP) involving the SCCS infrastructure. Any use of the SCCS data for research purposes has to be submitted to the SCCS Scientific Committee. This has to be done before initiating the project, to avoid duplication and potential conflicts with ongoing or already planned projects. SNP must be reviewed by the SCCS Scientific Committee also when they are going to be submitted to the Swiss National Science Foundation (SNSF) for funding. In this case, the prior approval by the SCCS Scientific Committee is a prerequisite for submission to the SNSF. In case of SNP not necessitating funding or SNP already funded by sources other than the SNSF, the positive decision of the SCCS Scientific Committee is sufficient for starting the work. If an SNP is nested within another research project already financed by the SNSF, the SCCS Scientific Committee must have the possibility to read the grant previously submitted to the SNSF and have full knowledge of its relative decision.

SNPs may be submitted by all researchers who are formally involved and actively participate in the SCCS or – if not members of the SCCS - committed to actively collaborate with the SCCS.

There are no fixed deadlines for submission. However, whenever a request is planned to be submitted to the SNSF, it is strongly advised to request a prior approval from the SCCS Scientific Committee at least 4 (four) weeks before the deadlines established for grant applications to the SNSF (i.e. September 30 and March 31).

In order to simplify the procedure of application for research projects, the Scientific Committee

supports the following types of SNP:

- Letter of Intent (LOI) (max. 3 pages)
- Full Proposal (with the detailed budget requirements, collaborations, other sources of funding)

All documents have to be submitted electronically (as pdf files) to the Chairperson of the Scientific Board, Dr David Semela, Klinik für Gastroenterologie und Hepatologie, Kantonsspital St. Gallen, Rorschacherstrasse 95, 9007 St.Gallen, Phone +41-71-4941216, e-mail David.Semela@kssg.ch

10.3 Letter of Intent

The LOI has the role of providing the submitting investigators with a preliminary assessment of the feasibility and scientific merit of a project nested within the SCCS and that can be later submitted as a Full Proposal. The LOI will include a short general description of the research question, the rationale and the resources likely to be needed. Minimum requirements include :

- a short introduction with 1 - 5 key references
- the study objectives
- the study design
- a preliminary budget

10.4 Full Proposal

The detailed description of the study should concisely present all the information necessary to allow a complete assessment of the proposal. It must be typed on no more than 10 pages. The following information is required:

- **Abstract** (max. one page)
- **Research plan** (present state of knowledge in the area of the proposed research with key references, followed by the objectives of the project in relation to state of knowledge)
- **Own research in the field**, including relevant experience and a list of publications, as well as relevant background information on the other investigators
- **Detailed research plan**, including the hypothesis to be tested, the study design (endpoints, inclusion and exclusion criteria), the investigations and tests to be performed in patients, the laboratory assays and methods, the drug information (if applicable), the follow-up evaluation and any specific patient management issues, the ethical committee evaluation, and all relevant biostatistical methods
- **Significance of the project**
- **Time frame**, whereby the research tasks to be performed within the credit and the duration of the projects should be explicitly mentioned
- **Available means and other sources of funding**, stating what infrastructure and manpower are already available for the study, and what funds you expect to obtain from other sources
- **Detailed budget**, including appropriate details as well as external funded expenses, the requested personnel position(s) and duration as justified by a description of the respective tasks, the keys of the financial distribution between the different participating centers; the budget of the study should take into the following costs: personnel, laboratory tests, specimen retrieval from the SCCS repositories (9 CHF per each sample), special tasks requested from the Data Center (data extraction and analysis), other expenses

10.5 Publication policy

A proposal for authorship should be part of each submitted project. It is understood that all authors have agreed to participate actively in the research proposal, have contributed (or will contribute) to the writing of the manuscript, and will approve its final version. For each project, the financial responsibility should be explicitly mentioned and the project should be approved by the chief of the unit, laboratory, etc. who is ultimately responsible for the advancement of the project.

All manuscripts of a certain importance and based on a substantial contribution of the SCCS – in terms of data and/or samples – should list at least one member of each study site as coauthor. These papers should also list up to three laboratory responsible persons (section 1.4), chosen based on a rota by Prof. Meri Gorgievski. Whenever the contribution of the SCCS is limited, the Scientific Committee may propose up to three coauthors chosen based on a rota.

The SCCS is listed as author in all manuscripts using the quote: *and the Swiss Hepatitis C Cohort Study Group*, followed by an index that refers to a footnote providing a full list of the SCCS Principal

Investigators (section 1.2) and other privileged participants as follows: Francesco Negro, Laurent Kaiser (Geneva); Markus Heim, Hans Hirsch (Basel); Jean-François Dufour, Meri Gorgievski (Berne); Darius Moradpour, Vincent Aubert (Lausanne); Hans H. Siegrist (La Chaux-de-Fonds); Andreas Cerny, Gladys Martinetti Lucchini (Lugano); Raffaele Malinverni (Neuchâtel); David Semela, Patrick Schmid, Günter Dollenmaier (St. Gallen); Beat Müllhaupt, Elsbeth Probst-Mueller (Zurich); Thomas Fabbro, Marielle Rudquist, Pascal Benkert (Basel Clinical Trial Unit).

10.6 Attachments to the research proposal

Please attach whatever information you feel would help support the submission of each research proposal. Such information may include:

- a cover letter
- the curriculum vitae of the principal investigator
- an informed consent form/patients' information form for all clinical trials
- Case Record Forms for clinical trials
- approval of the sponsoring institution's and/or the university's ethics review board
- list of potential reviewers (positive and negative, with reasons to exclude some of them)
- statement concerning the dissemination of results.

10.7 Evaluation and decision process

The SCCS Scientific Committee has to evaluate all submitted projects. The detailed procedure is decided internally by the Chairperson. The latter may appoint one or two external referees (including experts from abroad) in case of controversy among the internal members of the Scientific Committee about the decision to be taken. After the Scientific Committee has made its decision, this is notified by the Chairperson to the responsible investigator in a written and detailed form.

Authors who do not agree with the rejection of a project can appeal to the Scientific Committee within one month of the decision with a letter detailing the reasons for the rebuttal. The SCCS Scientific Committee will decide whether a further evaluation is warranted, but the following decision – in this case – has to be considered as definitive.

A grant application to the SNSF requires a prior approval by the SCCS Scientific Committee: the latter approval must be submitted together with the application. In this case, it is understood that (i) a preapproval by the SCCS Scientific Committee by no means constitutes a guarantee that the SNP will be fully or partially accepted by the SNSF, and that (ii) the submitting investigator is fully responsible – from both the administrative and scientific point of vue – of his/her project vis-à-vis the SNSF, and accepts to adhere to the guidelines established by this same institution concerning the grant allocation and subsequent evaluation.

10.7 Progress reports

A copy of the scientific report of each SNP must be made available upon request to the SCCS Scientific Committee, who will include a summary of the most relevant results on the SCCS website. The SCCS Scientific Committee reserves the right to issue recommendations in case the scientific work does not proceed as planned.

10.8 Special funding requirements

The SCCS Scientific Committee reserves the right to modify the SNP budget concerning (i) the SCCS clinical samples retrieval, and (ii) the costs for involving the Data Center personnel (data extraction, analysis), if deemed insufficiently covered at the time of submission.

10.9 Dissemination of results

The responsible investigator for each SNP has to state how he/she plans to disseminate the results of his research in a publicly available format (publication in scientific journal, thesis, communication at a scientific meeting), and this at the time of the initial submission of the SNP.

11. FUNDING AND SUPPORT

11.1 Funding

The SCCS routine functioning is mainly supported by the Swiss National Science Foundation, the Swiss Hepatitis C Cohort Study Foundation and other profit and non-profit parties, if necessary. Any nested and spin-off scientific study planning to exploit the data and samples collected during the study are in principle supported by funds managed by the single investigators responsible for these studies. Periodical activity reports are provided to main funding parties.

11.2 Other Support

The running costs of the SCCS are mostly contributed by the study centers. Local study nurses are partially paid by third parties (pharmaceutical industries and other financial sources). Some baseline costs, such as the e-CRF set-up and maintenance are guaranteed via a contract between the Foundation and the CTU of Basel University. The nested research projects are all funded by specific grants obtained by each single investigator (from the SNF or other sources). The hosting study institutions provide (i) the ambulatory care units where the patients' visits are carried out, together with all the diagnostic and therapeutic procedures; (ii) the salary of the applicants for the time dedicated to this project, and (iii) most of the infrastructure related to its appropriate implementation. The 8 Principal Co-Investigators at the clinical centers will support all the costs for (i) the data extractions (from the Basel CTU database) and biosample retrieval (from each peripheral repository) necessary for the nested scientific projects; (ii) the actual costs of the nested projects themselves, including salaries for the research assistants, PhD students and post-doctoral positions and all the consumables, via independent grant applications.

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13. ANNEXES

- Standard Operating Procedure for **blood sample collection**
- Standard Operating Procedure for **biosample handling**. i.e. evaluating the feasibility of a study and to obtain data and biosamples from the Basel CTU
- French and German handbooks containing the Standard Operating Procedure for **data collection**