FONDAZIONE EPATOCENTRO TICINO

Swiss Autoimmune Hepatitis Cohort Study

Research Plan

Type of Research Project:	Research project in which biological material is sampled from humans and health-related personal data is collected for research.
Risk Categorisation:	A
Project Identifier:	SASL 38
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Institution	Fondazione Epatocentro Ticino Via Soldino 5 6900 Lugano
Health condition	Autoimmune hepatitis (AIH)
Project Duration	At least 5 years
Project Plan Version and Date:	Version1.6, 16.05.2022

CONFIDENTIAL

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SIGNATURE PAGE(S)

Project Title Swiss Autoimmune Hepatitis Cohort Study

The Principal Investigator has approved the research plan version 1.6 16.05.2022, and confirm hereby to conduct the project according to the plan, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines and the local legally applicable requirements.

Principal Investigator:
PD Dr. med. Benedetta Terziroli Beretta-Piccoli

_____ _____
Place/Date Signature

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 Co-Investigators.

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SYNOPSIS (SUMMARY)

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Project Title:	Swiss Autoimmune Hepatitis cohort Study
Project Plan Version and Date:	Version 1.6,16.05.2022
Risk categorisation:	Risk category A
Type of Research:	Research project in which biological material is sampled and health-related personal data is further used and collected. Coded data are used.
Project design:	retrospective and prospective cohort with biobank.
Background and Rationale:	Autoimmune hepatitis is a rare inflammatory liver disease of unknown origin, affecting both children and adults. No standard second-line treatment schedules for difficult to treat patients exist. No data about the disease epidemiology, treatment schedules, response to treatment and overall outcomes exist from Switzerland.
Objectives:	To collect high quality prospective data on a rare disease in order to elucidate epidemiology, natural history, response to treatment and outcome. In addition, a biobank allows addressing specific scientific issues on a variety of open questions. The cohort will provide a platform for carrying out scientific research projects on AIH. In addition, the cohort will allow collaborations with reference networks on AIH abroad.
Inclusion / Exclusion criteria:	Inclusion criterion is diagnosis of AIH (1), either type I or type II. Only patients living in Switzerland are enrolled. Enrolment of minors is possible upon consent of legal guardian.
Measurements and procedures:	Enrolment visit and one follow-up visit at least once a year are planned. An additional follow-up visit at 6 months post-diagnosis is planned for newly diagnosed patients. Whole blood is collected for biobanking once a year Optionally, if available and collected during normal clinical procedures, liver fragments are obtained.

Number of Participants:	Number of subjects projected for the entire study (all sites combined): 500 (corresponding to 1/3 of the estimated global AIH population residing in Switzerland, assuming a disease prevalence of 20:100,000)
Project Duration, schedule:	The project will start by 1.1.2017. Estimated duration for the main investigational plan: at least 5 years.
Project Centres:	Multi-centre project, including 21 centres throughout Switzerland.
Risk-Benefit statement:	This project has no risk for participants; biosamples will only be collected concurrently with planned blood collection/liver biopsy for clinical purposes.

ABBREVIATIONS

Provide a list of abbreviations used in the project plan

AIH	Autoimmune Hepatitis
CEC	Competent Ethics Committee
CTU	Clinical Trial Unit
EC	Ethics Committee
e-CRF	Electronic Case Report Form
EDC	Electronic Data Capture
ERN	European Reference Network
FOPH	Federal Office for Public Health
GCP	Good Clinical Practice
HRO	Ordinance on Human Research with the Exception of Clinical Trials (Human Research Ordinance, HRO)
IAIHG	International Autoimmune Hepatitis Group
iAS	interactive Systems GmbH
ICF	Informed Consent Form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
LOI	Letter of Intent
LTFU	Lost To Follow Up
LTFUP	Lost to Follow UP
PBC	Primary Biliary Cholangitis
PSC	Primary Sclerosing Cholangitis
SNP	Scientific Nested Projects
SNSF	Swiss National Science Foundation
SOP	Standard Operating Procedure
UK-PBC	United Kingdom Primary Biliary Cholangitis

SCHEDULE OF ASSESSMENTS (FLOW OF RESEARCH PROJECT)

Project Periods	Screening				
Visit	1	2	3	4	…..
Time (month)	0	12	24	48	…..
Participant Information and Informed Consent	x At age 14				
Legal representative Information and Informed Consent for participants aged < 14					
Demographics	x				
Medical History	x	X*	X*	X*	X*
Inclusion Criteria	x				
Physical examination	x	X*	X*	X*	X*
Vital signs	x	X*	X*	X*	X*
Treatment history	x	X*	X*	X*	X*
Biochemistry	x	X*	X*	X*	X*
Liver autoantibodies	x	X*	X*	X*	X*
Immunoglobulin G	x	X*	X*	X*	X*
Sampling of biological material	x	X*	X*	X*	X*

For newly diagnosed subjects, an additional visit 6 months after diagnosis is planned.
For subjects aged 14-18, a consent form using a simple lay wording
* For subjects considered “relapse” by clinical judgement.

1. ADMINISTRATIVE STRUCTURE

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2. ETHICAL AND REGULATORY ASPECTS

2.1 Ethical Conduct of Study

The study is carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki (2), the guidelines of Good Clinical Practice (GCP) (3) issued by ICH, the Swiss Law and Swiss regulatory authority's requirements (4) (5). The EC and regulatory authorities will receive annual safety and interim reports and be informed about study end in agreement with local requirements.

2.2 Risk categorisation

The risk categorisation of the present project is A, according to HRO art.7.

2.3 Ethics Committee (EC) and Competent Authorities (CA), FOPH

Before the project will be conducted, the project plan and the proposed participant information and consent form will be submitted to the Ethics Committee Ticino, which will be the lead EC. Subsequently, the project will be submitted by the project coordinator to all others Swiss EC.

2.4 Declaration of interest

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

2.5 Participant 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 will be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All subjects 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 (Swiss AIH cohort consent) will be submitted to the CEC to be reviewed and approved. The formal consent of a participant, using the approved consent form, will be obtained before the subject is submitted to any study procedure. The subject reads and considers the documentation before signing and dating the informed consent form, and will be given a copy of the signed document. The consent form will also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

In case of participation to nested projects requiring the collection of additional biological samples (different kind of samples and/or at additional time points), a supplementary informed consent form will be submitted to patients, and their formal consent obtained before the subject is submitted to any extra procedure.

Autoimmune hepatitis can affect all age groups (1). In children, the disease has a more aggressive course, and overlap with autoimmune sclerosing cholangitis is present in a high proportion of patients (6). For these reasons, the present study will include children as well. Adolescents aged 14 and over will receive a verbal briefing and written information with the same content as that given to their legal representative, but using a simple lay form of consent. Since the present study only entails minimal risks and burden, the signature of their legal representative is not required. Children with a developmental age of 11-13 years will be given a verbal briefing and written Patient Information that has been adapted to this age group's comprehension level. Their legal representatives will receive all the information. The legal representatives will provide their consent on the same consent form as that used to confirm that a verbal briefing has been given. Children with a developmental age 10 years or under will be briefed verbally. Their legal representatives will receive all the information and provide their consent on the same consent form as that used to confirm that a verbal briefing has been given. If the subjects are neonates, infants and toddlers, it will not be possible to brief them. Their legal representatives will receive all the information and provide their consent. For children enrolled before age 14, with the ICF signed by their legal representatives, it is required that they are given the ICF for adolescents aged 14-18 when they turn 14, with appropriate verbal briefing. This ICF must be signed by the adolescent, in order to obtain the consent for the participation in the study by the patient himself.

2.6 Participant privacy and safety

Individual subject medical information obtained as a result of this study is considered confidential. Subject confidentiality is ensured by utilising subject identification code numbers when personal data are entered in the electronic case report forms (e-CRFs). Anonymity of the participants is guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.
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.

2.7 Early termination of project

The project coordinator (and any competent authority) may terminate the project prematurely in case of insufficient participant recruitment, or in case of financial issues.

2.8 Amendments, Changes

Significant changes to the project plan must be approved by the EC (amendments).
The project coordinator shall submit to the EC any application documents specified in, which are affected by the change. At the same time, the project coordinator shall provide information on the reasons for the change. Substantial amendments are only implemented after approval of the EC.

3. INTRODUCTION

3.1 Background

Autoimmune liver diseases are rare, inflammatory hepato-biliary conditions. Among these, the three most frequent are primary biliary cholangitis (hitherto cirrhosis) (PBC), autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC). Overlap between AIH and both of the diseases involving the biliary tract also exist (7). Patient morbidity and mortality remain high across these three diseases, and an unmet need for rational therapy exists.

Autoimmune hepatitis is a severe life threatening chronic progressive immune-mediated inflammatory disorder of the liver (1). The aetiology of AIH is largely unknown, but liver damage is believed to be the consequence of an aberrant immune response to an as yet unknown antigen in a genetically predisposed host (8). To date, little is known about the genetic and immunological factors underlying disease susceptibility. In all but the mildest form of AIH, fibrosis is frequently present at diagnosis, and with advanced disease bridging fibrosis and cirrhosis are often seen. More than 50% of patients have fibrosis at diagnosis and up to 20% have cirrhosis, which indicates that the disease has remained unrecognized for a significant period of time (9). Over the past four decades there has been only marginal development of novel therapies in AIH, current treatment schedules dating back to the mid-seventies (1,10). Such treatments include the long-term use of predniso(lo)ne, which not always arrests disease progression and has severe side effects. The slow progress both in terms of understanding disease pathogenesis and in the development of novel treatments has resulted in outdated guidelines. This stems from the fact that AIH is a relative uncommon disease, which has received limited interest from pharmaceutical companies and the scientific community (11,12).

3.2 Rationale for the research project

Rare disease patient cohorts represent a fundamental research effort upon which a number of critical activities are based. They constitute key instruments for increasing knowledge on rare diseases by pooling data for basic and clinical research, epidemiological research, and real-life post-marketing observational studies.

The present retrospective and prospective data collection will allow to gain insights into the incidence, pathogenesis, natural history, response to first-, second-, third-line therapies and overall outcomes of AIH in Switzerland. No standard second- and third-line therapies for AIH exist, and patients with an insufficient response or intolerant to first line therapy, are treated with heterogeneous schedules. An additional major advantage of the present project is to allow conducting nested projects (see section 10.2). The International AIH Group (IAIHG, http://www.iaihg.org) has initiated a international registry enrolling AIH patients of all ages. Data from the present project will be shared with the IAIHG registry (Appendix 1) in coded form. This will happen also for the prospective registry in the context of ERN (European Reference Network). Similar initiatives abroad in the field of autoimmune liver diseases have demonstrated the utility of this kind of data collection. In particular, a nationwide cohort study on PBC patients has been set up in 2007 in the UK (UK-PBC): this cohort includes every hospital providing general or specialist hepatology services, as well as the only major liver treatment centre in Northern Ireland. This cohort has significantly contributed to our understanding of the disease. As an example, recently, a prognostic score has

been proposed based on the data obtained from this cohort (13). A similar score has been recently developed by another, international PBC cohort (14).

3.3 Risk-Benefit Assessment

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

4. OBJECTIVES

The specific objectives of this project are to establish a unified Swiss web-based cohort for prospective high-quality baseline and follow-up data registration of AIH patients according to standardised directives. This will allow investigators to elucidate epidemiology, clinical presentation, natural history and outcomes of the disease. Outcomes of second- and third-line treatment regimens are of particular interest. The biobank will allow investigators to carry out genetic, serological and immunological studies. Since AIH is a rare disease and Switzerland is a small country, strong collaboration with similar cohorts abroad will allow Switzerland to participate in projects requiring large number of patients, and to be part of the expertise of the international framework in the field of autoimmune liver diseases. This will ultimately improve the quality of the care delivered to the patients. For this reason, patients enrolled in the Swiss AIH Cohort, will be enrolled in the IAIHG registry as well, provided they meet inclusion criteria. This will happen also for the prospective registry in the context of ERN (European Reference Network), led by Professor Christoph Schramm, Hamburg, Germany.

5. PROJECT DESIGN

5.1 Type of research and general project design

This is a nationwide multicentre observational retrospective and prospective data and biosample collection.

5.2 Procedures

Persons fulfilling the eligibility criteria are assigned a 6-digit code at enrolment. Thus, all data and material are coded. The list of codes is kept by each single participating investigator.

At enrolment and at each follow-up visit, data on demographic characteristics, liver disease staging, signs of cirrhosis, bone mineral density, treatment history, liver transplantation, liver malignancies, death and, for patients up to 18 years of age, Tanner pubertal stages are collected. In addition, a full panel of blood test results is collected, including biochemistry, serological assays for liver autoantibodies and immunoglobulin G.

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. Each enrolled study participant has a dedicated e-CRF page. CRFs are completed by clinicians once a year (additional visit at 6 months post diagnosis for newly diagnosed patients). The collaboration with the CTU Basel is deemed crucial to ensure the standardization of the data collection and quality and consistency of the database. For patients enrolled in the IAIHG registry and the ERN registry, the bespoken eCRF managed by Castor will be completed as well.
In addition to the clinical data, the Swiss AIH cohort collects at every study visit a blood sample, stored in the form of serum and PAXgene at repositories centrally located at Epatocentro Ticino, in Lugano. In selected patients, heparin blood, urine, plasma (about 10 mL) and faces can be collected as well, and stored at Centro di Immunologia Medica, Istituto di Ricerca in Biomedicina, Università della Svizzera Italiana, Bellinzona. Storage follows standard biobanking criteria of quality. Any investigator (or group of investigators) can access the Swiss AIH cohort data for research projects, pending the approval – based on feasibility and scientific merits – of the Scientific Committee, following the procedures outlined below (section 10).

5.3 Recruitment and Screening

Patients are enrolled at each study center by one of the local co-Investigators or one of his/her delegates provided that the latters have had 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' data are coded by assigning to each patient a unique 6-digit code. The list of codes is kept by each single participating investigator. Duplicate enrolments are ruled out by identifying each patient with the 6-digit code and his/her sex and height (for subjects aged > 18 years).
Participants are not given any payment or any sort of compensation for medical and other costs incurred during the time of participation to the cohort. 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 AIH according to the state-of-the-art knowledge in the field: thus, the cost of these medical procedures are paid for by each patient's medical insurance. No additional interventions – diagnostic or therapeutic – are required in association with the participation to the Swiss AIH cohort. Patients are requested only to allow the collection of their blood in the total amount of maximum 38 ml once a year (a smaller amount of blood is collected for children, see 7.2), but the material and the procedures associated with this are entirely free of charge.

6. PROJECT POPULATION

Based on epidemiologic population-based studies on AIH (11,12,15) in other Western countries, the expected prevalence of AIH in Switzerland is between 12 and 25 cases per 100'000 people, with a total number of cases between 1000 and 2000 in the whole

Switzerland. We expect recruiting about 100 patients initially, and the number will increase by including incident cases.

6.1 Inclusion criteria

All AIH patients living in Switzerland of any age can be included in the cohort. The diagnosis of AIH is made according to well established criteria (16). However, such criteria can miss atypical cases (1), which are of particular interest for the cohort. As a consequence, patients not fulfilling such criteria but still diagnosed with AIH in a hepatology referral centre can be included.

6.2 Criteria for withdrawal of participants

Patients are withdrawn from the study in the following cases:

- The patient has stably emigrated to another country;
- The patient has explicitly declared his/her unwillingness to continue (opt-out);
- The patient has not responded to at least two written invitations, after failing to attend for follow up for 24 months from the latest visit: in this case, the patient must be withdrawn. However, this must be a last resort procedure, since all efforts should be made to contact patients who fail to attend the annual visit, to evaluate timely the disease course and possible need for second- or third-line therapies.

In the above circumstances, the investigator or his-her delegates will fill the appropriate form designated as Stop/Re-Entry in the electronic database.

6.3 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 should be entered in the e-CRF.

6.4 Change of study centre

Patients who move within Switzerland and are followed up at a new study center will not change their subject identification code number 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 previous and the new study center. .

6.5 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 6.2) 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 informed consent form (ICF) whereby the patients accept this procedure at the act of enrolment.

6.6 Trial specific preventive measures

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

7. PROJECT ASSESSMENTS

7.1 Project flow chart

See SCHEDULE OF ASSESSMENTS

7.2 Biosampling

At each routine study visit and for subjects considered “relapse” by clinical judgement, whole blood is collected for storage, in addition to routine diagnostic assays.
The amount of blood is established as follows:

1. **Serum**: one 5 ml tube with serum separator to prepare 4 aliquots of serum (each of 0.5 ml). For children < 20kg body weight, a 3.5 ml tube will be used.

2. **mRNA:** one 2.5 ml PAXgene Blood RNA tube, to be stored at -80°C as it is.

In selected patients, following samples can also be collected:
3. **Viable cells:** three 10 ml heparin tubes for adults and subjects with body weight > 40 kg, one 10 ml heparin tube for children with body weight between 20 and 40 kg, one 6 ml heparin tube for children with a body weight < 20 kg.
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.
Blood samples will be stored centrally at the Epatocentro Ticino in Lugano. Liver biopsies will be stored locally. Viable cells, plasma, urine and faces will be stored at Centro di Immunologia Medica, Istituto di Ricerca in Biomedicina, Università della Svizzera Italiana, Bellinzona.
If requested for a specific nested project (see 10.2), different kind of blood samples and at different time points can be collected. Similarly, urine, faeces and other biological samples can be collected if requested by a specific nested project.

7.3 Safety

Not applicable to this study.

8. STATISTICAL METHODOLOGY

8.1 Determination of Sample Size

The study plans to enrol a total of 500 AIH patients in three years. This corresponds to about 30% of the estimated total AIH population in Switzerland, assuming a disease prevalence of 20:100,000 inhabitants.

8.2 Handling of missing data

Despite a carefully planned and conducted study, some data will be missing and participants will drop out. Missing data is a potential source of bias, but there is no universal best approach for handling this. In case of substantial quantity 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.

9. DATA AND QUALITY MANAGEMENT

9.1 Data handling and record keeping / archiving

The clinical trial data will be collected in the electronic data capture (EDC) system named secuTrial (interActive Systems GmbH (iAS), Berlin).
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 data management group at the Clinical Trial Unit (CTU) at the University Hospital Basel.
The electronic data capture system of the retrospective IAIHG Registry and the ERN registry is named Castor (see appendix).

9.2 Confidentiality, data protection

Data generation, transmission, storage and analysis of health-related personal data and the storage of biological samples within this project will follow strictly the current Swiss legal requirements for data protection and will be performed according to the Ordinance HRO Art. 5.
Coding will safeguard participants' confidentiality.
Some samples can be anonymized (no name and no code) before sending to other laboratories and institutions.
Project data shall be handled with uttermost discretion and only be accessible to authorised personnel. Direct access to source documents will be permitted for purposes of monitoring, audits or inspections and should declare who will have access to project plan, dataset, statistical code, etc. during and after the research project (publication, dissemination).

9.3 Data security, access and back-up

Password protection ensures that only authorized people 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.

10.4 Coding

Subjects fulfilling the eligibility criteria are assigned a 6-digit code at enrolment. Thus, all data and material are coded. The list of codes is kept by each single participating

investigator. 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 six alphanumeric digits. The first two digits identifies the study center:
01= Epatocentro Ticino
02= Universitätsspital Zürich
03= Inselspital Bern
04= Kantonsspital Baselland
05= Kantonsspital St.Gallen
06= Hôpitaux Universitaires de Genève-Service de Gastroenterologie & Hépatologie,
07= Hôpitaux Universitaires de Genève-Centre Suisse des Maladies du foie de l'Enfant- Département de l'Enfant et de l'Adolescent
08= Kinderklinik, Inselspital BERN
09= Universitäts-Kinderspital beider Basel (UKBB)
10= Kantonsspital Graubünden Chur, Departement für Kinder- und Jugendmedizin
11= Luzerner Kantonsspital I Kinderspital
12= Ostschweizer Kinderspital St. Gallen, pädiatrische Gastroenterologie und Ernährung
13= Universitäts-Kinderspital Zürich – Leiter Abteilung Gastroenterologie und Ernährung
16= Kantonsspital Winterthur – Winterthur
17= Kindespital Kantonsspital Winterthur – Winterthur
18= CHUV Département femme-mère-enfant – Lausanne
19= Universitätsspital Basel, PD Dr. med. Dr. phil. Christine Bernsmeier, Gastroent. und Hepat.Clarunis
20= EOC Institution: EOC Ospedale Regionale di Lugano – Italiano, Prof Dr. med Andrea De Gottardi
21= Spital Bülach - PD Dr. med. Stephan Böhm

The coding key will be kept in each centre. Designated people have access to the coding key in their own centre.

9.5 Analysis and archiving

Data extraction and analysis for scientific projects are performed by the CTU data centre after that 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.

9.6 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 centre upon request. Identified inconsistencies are communicated and solved by means of queries within the EDC system.

10. PUBLICATION AND DISSEMINATION POLICY

The results of studies carried out using medical data and biosamples collected within the setting of the Swiss AIH cohort will form the object of scientific publications (presentations at scientific conferences, manuscripts to be submitted to journals with or without editorial policy).
The access to the resources will be subjected to approval – based on scientific merit and feasibility – by the scientific board.
All manuscripts of a certain importance and based on a substantial contribution of the SwissAIH cohort – in terms of data and/or samples – should list at least one member of each study site as co-author. Whenever the contribution of the Swiss AIH cohort is limited, the Scientific Committee may propose up to three co-authors based on their involvement in the project.

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10.2 Guidelines for scientific nested projects

The Swiss AIH cohort welcomes all research in the form of Scientific Nested Projects involving the cohort infrastructure. Any use of the Swiss AIH cohort data for research purposes has to be submitted to the Scientific Committee. This has to be done before initiating the project, to avoid duplication and potential conflicts with on-going or already planned projects. SNP must be reviewed by the Swiss AIH cohort 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 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 Scientific Committee is sufficient for starting the project. If an SNP is nested within another research project already financed by the SNSF, the Scientific Committee must have the possibility to read the grant previously submitted to the SNSF and have full knowledge of its related decision. SNPs may be submitted by all researchers who are formally involved and actively participate in the Swiss AIH cohort or – if not members of the Swiss AIH cohort - committed to actively collaborate with the Swiss AIH cohort.
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 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.

Biosamples and data will be completely anonymized (no name and no code, only a number in ascending order assigned by the CTU) before sharing them with third parties.

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 Swiss AIH cohort, which 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 current 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, 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 technical support and other sources of funding, stating what infrastructure and manpower are already available for the study, and what funds are expected from other sources
- Detailed budget, including appropriate details as well as external funded expenses the requested personnel position(s) and duration justified by a description of their respective tasks, the keys of the financial distribution between the different participating centers. The budget of the study should take into account the following costs: personnel, laboratory tests, specimen retrieval from the Swiss AIH cohort repositories, 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 will have agreed to participate actively in the research proposal, will 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 director 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 Swiss AIH cohort – in terms of data and/or samples – should list at least one member of each study site as co-author. Whenever the contribution of the Swiss AIH cohort is limited, the Scientific Committee may propose up to three co-authors based on their involvement in the project.
The Swiss AIH cohort is listed as author in all manuscripts using the quote: *and the Swiss AIH Cohort Study Group*, followed by an index that refers to a footnote providing a full list of the Principal Investigators (section 1), the scientific board members (section 10.1) and other privileged participants.

10.6 Attachments to the research proposal

Please attach whatever information you feel would help support the submission of the research proposal. The following information must be provided:

- a cover letter
- the curriculum vitae of the principal investigator and co-investigators
- 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 Swiss AIH Cohort Scientific Committee will evaluate all submitted projects. A detailed evaluation 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 Swiss AIH Cohort Scientific Committee will decide whether a further evaluation is warranted, but the following decision – in this case – will be definitive.
A grant application to the SNSF requires a prior approval by the Swiss AIH Cohort Scientific Committee: the latter approval must be submitted together with the application. In this case, it is understood that (i) a preapproval by the Swiss AIH Cohort 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 view – 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.

10.8 Progress reports

A copy of the scientific report of each SNP must be made available upon request to the Swiss AIH cohort Scientific Committee. The Scientific Committee reserves the right to issue recommendations in case the scientific work does not proceed as planned.

10.9 Special funding requirements

The Swiss AIH cohort Scientific Committee reserves the right to modify the SNP budget concerning (i) the Swiss AIH cohort 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.

10.10 Dissemination of results

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

11. FUNDING AND SUPPORT

The present project is partially founded by the Fondazione Epatocentro Ticino and as an Investigator Initiated Trial by third parties.

12. REFERENCES

1. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Autoimmune hepatitis. J Hepatol. 2015 Oct;63(4):971–1004.
2. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013 Nov 27;310(20):2191–4.
3. EGEP_en.pdf [Internet]. [cited 2016 Jun 15]. Available from: http://www.public-health.ch/logicio/client/publichealth/file/EGEP_en.pdf
4. Bundesamt für Gesundheit - Bundesgesetz über die Forschung am Menschen [Internet]. [cited 2016 May 8]. Available from: http://www.bag.admin.ch/themen/medizin/00701/00702/07558/index.html?lang=de
5. CC 810.301 Ordinance of 20 September 2013 on Human Research with the Exception of Clinical Trials (Human Research Ordinance, HRO) [Internet]. [cited 2016 Jun 15]. Available from: https://www.admin.ch/opc/en/classified-compilation/20121177/index.html
6. Mieli-Vergani G, Vergani D. Sclerosing Cholangitis in Children and Adolescents. Clin Liver Dis. 2016 Feb;20(1):99–111.
7. Lohse AW, zum Büschenfelde KH, Franz B, Kanzler S, Gerken G, Dienes HP. Characterization of the overlap syndrome of primary biliary cirrhosis (PBC) and autoimmune hepatitis: evidence for it being a hepatitic form of PBC in genetically susceptible individuals. Hepatol Baltim Md. 1999 Apr;29(4):1078–84.
8. Longhi MS, Ma Y, Mieli-Vergani G, Vergani D. Aetiopathogenesis of autoimmune hepatitis. J Autoimmun. 2010 Feb;34(1):7–14.
9. Manns MP, Czaja AJ, Gorham JD, Krawitt EL, Mieli-Vergani G, Vergani D, et al.

Diagnosis and management of autoimmune hepatitis. Hepatol Baltim Md. 2010 Jun;51(6):2193–213.
10. van Gerven NMF, Verwer BJ, Witte BI, van Hoek B, Coenraad MJ, van Erpecum KJ, et al. Relapse is almost universal after withdrawal of immunosuppressive medication in patients with autoimmune hepatitis in remission. J Hepatol. 2013 Jan;58(1):141–7.
11. Boberg KM. Prevalence and epidemiology of autoimmune hepatitis. Clin Liver Dis. 2002 Aug;6(3):635–47.
12. van Gerven NMF, Verwer BJ, Witte BI, van Erpecum KJ, van Buuren HR, Maijers I, et al. Epidemiology and clinical characteristics of autoimmune hepatitis in the Netherlands. Scand J Gastroenterol. 2014 Oct;49(10):1245–54.
13. Carbone M, Sharp SJ, Flack S, Paximadas D, Spiess K, Adgey C, et al. The UK-PBC risk scores: Derivation and validation of a scoring system for long-term prediction of end-stage liver disease in primary biliary cholangitis. Hepatol Baltim Md. 2016 Mar;63(3):930–50.
14. Lammers WJ, Hirschfield GM, Corpechot C, Nevens F, Lindor KD, Janssen HLA, et al. Development and Validation of a Scoring System to Predict Outcomes of Patients With Primary Biliary Cirrhosis Receiving Ursodeoxycholic Acid Therapy. Gastroenterology. 2015 Dec;149(7):1804–12.e4.
15. Ngu JH, Bechly K, Chapman BA, Burt MJ, Barclay ML, Gearry RB, et al. Population-based epidemiology study of autoimmune hepatitis: a disease of older women? J Gastroenterol Hepatol. 2010 Oct;25(10):1681–6.
16. Hennes EM, Zeniya M, Czaja AJ, Parés A, Dalekos GN, Krawitt EL, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatol Baltim Md. 2008 Jul;48(1):169–76.

13. ANNEXES

- Protocol of the Registry ERN
- IAIHG Items
- Letter to Ethic Committee submitted by Prof. Dr. Schramm (Amendment PV 5548)
- Ethic approval R-LIVER
- Protocol of the retrospective IAIHG registry