Appendix 1.1 :

Study protocol

Pharmacologie médicale

Pharmaco-épidémiologie
CIC Bordeaux CIC1401

SALT-II

Study of Acute Liver Transplant

"Prolongation and continuation of the SALT-I study"

A study of drug-exposed acute liver failure
in European transplant centres

Study Protocol

Version: 3.0
7th March 2014

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HISTORY OF PROTOCOL UPDATES

Version	Date	Reason of update
V2.0	23/12/2013	Submitted version to regulatory authorities in France (CCTIRS, CNIL)
V3.0	07/03/2014	Amended version following the ENCePP Seal requirements

1 SUMMARY

Study General Information	
1. Title	SALT-II: Study of Acute Liver Transplant Prolongation and continuation of SALT-I study A study of drug-exposed acute liver failure (ALF) in European transplant centres
2. Study code	SALT-II
3. Phase	IV: Pharmacoepidemiological study
4. Products of interest	All drugs including herbal medicines
5. Study Rationale	The SALT-I study created a network of 55 liver transplant centres in seven European countries. It also accumulated a considerable body of data on drug-exposed acute liver failure in Europe. The national coordinators of these centres have expressed a desire to continue this collaboration and monitor severe acute hepatitis in Europe. Furthermore, the main objective of SALT-I concerned only the risks associated with NSAIDs. One of the main objectives of the SALT-II study is to assess the risks associated with other drugs than NSAID. The incidence of these very severe drug-induced acute liver failure is very low: we could identify only 40 cases associated with NSAIDs over 2005-2007, and fewer still with other drugs except paracetamol. To improve the precision of the measures of incidence, and to be able to identify emergent risks, it would seem desirable to increase the number of cases identified, by continuing the study for the next six years (2008-2013), and studying the possibility of expanding the network to other countries (Germany, Spain, Nordic or Eastern European countries).
6. Study design	Multicentre, multinational retrospective case-population study of patients exposed to drugs registered for liver transplantation because of ALF. As in the SALT-I study, the cases will be from the liver transplant units, after identification from national/local transplant registries. Data collection of the cases will be completed by trained clinical research assistants by seeking data through hospital medical files. Cases will be validated by trained hepatologists (National Case Selection Committee Hepatologist, NCSCH). The denominator will be drug exposure defined from drug sales obtained

	from a commercial data vendor (Intercontinental Medical Services, IMS) or from other sources where available.
7. Objectives: Primary Secondary	• To estimate the risk of Acute Liver Failure leading to registration for Transplantation (ALFT) in adults exposed to drugs, according to the population exposure to the same drugs. • To compare event rates between countries, for all drugs and for specific drugs. • To compare the effect of choosing different denominators (number of subjects, person-time, DDD) on the relative frequencies measured, and to measure the impact of choice of the exposure window of 7 to 90 days on the observed frequencies.
8. Assessment Parameters: Primary endpoint Secondary endpoints	Parameter definition: incidence rate of ALFT • The numerator of the incidence rate is the number of cases of ALFT where the patient has been exposed to the product of interest within 30 days before onset of signs or symptoms of the liver disease. • The denominator of the incidence rate is the estimated population exposed in the countries where the study is performed according to sales, prescription or dispensation data. Exposure is measured in number of DDD sold over the study period, number of patient-years (number of observed Prescribed Daily Doses sold over a year), and if available from population databases, the number of patients treated over the study period. • Global frequency of occurrence of the ALFT (without clinically defined cause) listed on the transplant list, in subjects exposed to a drug 30 days prior to index date (ID, date of the onset of the liver disease) in five European countries over the 6-year period (2008-2013). • The relative event rates within drugs of the same class. • Inclusion of data from the SALT-I to determine the overall frequency over nine years (2005-2013). • Frequency of occurrence measured using different denominators (number of subjects, number of DDD, number of patient-years). • Frequency based on the number of drug-exposed cases aged between 18 and 70 years (age range observed for subjects transplanted).

9. Participating countries and expected number of cases	There were very few or no drug-exposed cases of ALFT in Greece & Portugal; it is therefore proposed that SALT-II be restricted initially to the five main contributors to SALT-I: France, Ireland, Italy, the Netherlands, and the UK. The SALT-I study identified 363 drug-exposed cases of ALFT in the seven participating countries over the three-year study period, out of 600 cases of ALFT. Over the six years of SALT-II, it is expected that 1200 all-cause ALFT and 726 drug-associated ALFT will be identified, so that total numbers would reach 1800 ALFT and over 1000 drug-associated ALFT. If needed to improve representativeness or increase the power of the study, it could be extended to Spain, which already has an active network of DILI centres, to Germany, the largest European country in population size, to the Nordic countries and to Eastern European countries. Doubling the population base would double the number of cases, if the transplant activity is homogeneous over Europe.
10. Study period	The study will retrospectively evaluate a six-year period (1st January 2008 - 31st December 2013) (further to the study period of SALT-I study; 1st January 2005 – 31st December 2007).
11. Case definition	Eligibility criteria: - Adult patients of at least 18 years of age at the time of registration to the transplantation list, whether the transplantation is actually performed or not, - Patient with ALF registered for liver transplantation from 2008 - 2013, - Resident in the considered countries at the time of registration. Non-eligibility criteria: - Patients younger than 18 years of age, - Not resident in the selected countries.
12. Case identification	All patients registered for liver transplantation for any reason at eligible centres within the study period were identified through either national (France: CRISTAL; Ireland and UK: UK Transplant Registry; Netherlands: National Waiting List;) or local transplant lists (Italy).
13. Case selection	The case selection is a three-step process, done by the National Case Selection Committees: The first step of case selection will identify patients with ALF and those with diagnoses other than ALF (chronic liver failure, CLF), for which succinct demographic data will be collected.

	In the second step, patients with ALFT will be separated into those with (*i.e.* viral hepatitis, auto-immune hepatitis, etc.) or without an identified clinical cause. Patients with an identified clinical cause will not be further assessed for drug exposure. In the third step, ALFT patients without an identified clinical cause will be separated into acute drug overdose (with or without suicidal intent), exposure to drugs within 30 days prior to index date or no exposure to drugs, as confirmed by the NCSCH. For drug-exposed ALFT, all information on drug use will be documented under the control of the NCSCH and NCSCH will determine for each one the ID (date of the onset of the liver disease) and transmit his conclusions to the study coordinating centre
14. Case confirmation	The NCSCH will validate the data at each step of case selection confirming the clinical and laboratory case definition criteria.
15. Index date and exposure	The index date (ID) is the date of onset of liver disease (initial symptoms or laboratory evidence) and will be determined and validated by the NCSCH. For all drugs, including herbal medicines, the exposure window selected is within 30 days prior to ID. Other exposure windows (90, 15 and 7 days) will be used for sensitivity analyses.
16. Study Duration	Data collection will start once all necessary authorisations will be obtained.
17. Statistical analysis	<u>Main analyses:</u> • Descriptive analysis: A descriptive analysis of all drug-exposed cases of ALFT will be performed. • Rate estimations per country: Per country rates of drug-exposed transplantation registered ALF will be computed as the ratio of the number of cases identified in the country to the population exposure. Population exposure will be measured in treatment-years (source: IMS). The estimation of the rate of drug-exposed ALFT cases within 30 days prior to ID, with a 95% CI from a Poisson distribution, expressed in cases per million treatment-years. The frequency of ALFT will be calculated also for people aged 18 to 70 years. • Pooling: Data of SALT-II will be pooled with data of the previous SALT-I study to estimate the frequency of ALFT identified in nine years (2005-2013). This will allow a greater

	number of events and a better precision of the risk estimates. Sensitivity analyses: Sensitivity analyses will be performed using different sources of information to determine the size of populations at risk, based on sales data provided by IMS (primary analysis), data delivery (CNAM-TS Medicam data for France or equivalent in the other participating countries) and usage data determined from the information about the actual or theoretical use of products: for DDD (primary analysis), determined by DDD panels, depending on usage patterns identified by reimbursement (France) the basis of population data (*i.e.* Italy, the Netherlands, the UK) for taking as denominator the total consumption in DDD, in patient-years (PDD/365), or patient numbers (based on patterns of use). The study will include all drug families found present in at least five cases. Sensitivity analyses will also be performed for different exposure windows of interest (from 7 to 90 days). Statistical analyses will be carried out using SAS software (SAS Institute, North Carolina, USA, current version), following the analysis plan.
18. Study Committees	A steering committee (SC) composed of international experts in pharmacoepidemiology, hepatology will follow the scientific conduct of the study. In each participating country a coordinator (National Case Selection Committee Hepatologist, NCSCH) will be assigned to help with country-specific aspects, and validation of cases from their own country.
19. Ethics, Data Confidentiality, Patient Protection and Good Practices	This study will be done according to good pharmacoepidemiology practises as described by ISPE (www.pharmacoepi.org) and will comply with all relevant legislation concerning data protection. This study will be developed according to the European Network of Centres of Excellence in Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct and methodological standards guide, and the ENCePP seal will be sought for. Study protocol and results will also be made public according to ENCePP requirements.

20. Strengths and Limitations	The strengths of the SALT-II study are that it focuses on cases of ALFT, gives an estimate of absolute population-based event rates. Based on the liver transplant network created by SALT-I study, this cooperation will continue with the inclusion of new countries, allowing a European network (EURO-SALT) that enables real-time monitoring of liver transplants, according to the same model of population-based case surveillance. Furthermore, SALT-I study has already accumulated a considerable body of data on drug-exposed ALFT in Europe. SALT-II study will provide data for another six-year period, allowing to evaluating many other drugs, and gaining information over nine years.

TABLE OF CONTENT

2 STUDY PARTICIPANTS

The study participants include a Steering Committee that will monitor and accompany the study, and National Cases Selection Committee Hepatologist (NCSCH) that will follow the case selection process.

Representatives of the Study Project Team (Coordinating Centre) will be present at the committee meetings.

2.1 STEERING COMMITTEE

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2.2 NATIONAL CASE SELECTION COMMITTEE HEPATOLOGIST

The National Case Selection Committee Hepatologist will be designed for each country.

France	Prof. Georges-Philippe Pageaux
Ireland	To be defined
Italy	To be defined
Netherlands	To be defined
United Kingdom	To be defined

2.3 STUDY PROJECT TEAM (COORDINATING CENTRE)

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2.4 STUDY FINANCE

The SALT project is one of the objectives of the Bordeaux University Foundation Chair in Pharmacology, and as such may receive donations from industry through the Foundation.

3 ABBREVIATIONS

ALF	Acute Liver Failure
ALFT	Acute Liver Failure leading to registration for Transplantation
ATC	Anatomical Therapeutic Chemical
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLF	Chronic Liver Failure
CNIL	*Commission Nationale de l'Informatique et des Libertés* (National Commission on Informatics and Freedom)
CNOM	*Conseil National de l'Ordre des Médecins* (National Order of Physicians)
CMV	Cytomegalovirus
CRA (ERA)	Clinical (epidemiology) research assistant
CRF	Case Report Form
CRO	Contract Research Organisation
DDD	Defined Daily Dose
EBV	Epstein Barr Virus
ENCePP	European Network of Centres of Excellence in Pharmacoepidemiology and Pharmacovigilance
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HEV	Hepatitis E Virus
HSV	Herpes Simplex Virus
ID	Index Date
ISPE	International Society for Pharmacoepidemiology
NCSCH	National Case Selection Committee Hepatologist

NSAID	Non-Steroidal Anti-inflammatory Drug
PDD	Prescribed Daily Dose
OTC	Over-The-Counter
SC	Steering Committee
UK	United Kingdom
ULN	Upper Limit of Normal

4 INTRODUCTION

Acute liver injury has been reported with most drugs, and is one of the more common reasons for drug withdrawal from the market, or for interruption of development. (1-3)

Acute liver reactions range from the simple asymptomatic increase in liver enzymes, to liver transplantation. Asymptomatic increases in liver enzymes, mostly transaminase, are discovered through systematic monitoring of patients, as is done routinely during clinical development, but have no clear clinical safety implication. The usual limit for non-seriousness of increased transaminase is considered to be three times upper limit of normal (ULN). (4, 5) More severe reactions include "Hy's law" cases which combine transaminases above three times ULN, usually above 5 times ULN, with increased bilirubin above twice ULN, without cholestasis and without other causes of liver injury. The most severe cases result in liver failure and often death or liver transplantation. It is the latter cases that have the greatest public health importance.

Among different drug classes, non-steroidal anti-inflammatory drugs (NSAID) have often been involved in liver injury (6, 7) and adverse hepatic reactions have been reported for most NSAIDs. (8) General population studies of hepatic reactions with NSAIDs did not demonstrate a clear difference between NSAIDs for hepatic reactions not leading to transplantation. (9, 10) Because of a suspected greater risk of hepatotoxicity with nimesulide, the CHMP required an epidemiological study of the more severe NSAID-exposed acute liver failure in Europe, those leading to transplantation (ALFT).

This led to the SALT study (Study of Acute Liver Transplantation) whose objective was to assess the risk of ALFT, in patients without identified clinical aetiology, exposed to NSAIDs, in seven European countries. (11) Of the 57 eligible centres in the countries concerned, 54 (94.7%) accepted to participate: 20/21 in France, 19/20 in Italy, 2/2 in Greece, 3/3 in the Netherlands, 2/3 in Portugal, 1/1 in Ireland, and 7/7 in the UK. However, one centre in the UK and one in Italy could not provide data within the study timeframe because of administrative delays, (12) so that in fine 52/57 eligible centres contributed data (91.2%). These centres contributed over 90% of all registrations for liver transplantations, as determined from national registries. In these 52 contributing centres, 9479 patients were identified on liver transplantation waiting lists. Medical files were not available for 41 patients (0.4%); 8838 patients (93.2%) were listed for CLF and 600 (6.3%) for ALFT. For 18 ALFT patients (3.0%), the medical files were missing or incomplete, and case characteristics could not be ascertained. In 219 (36.5%), ALFT was explained by a defined clinical

aetiology, and these cases were not further explored for drug exposure. These were hepatitis B viral hepatitis (34.7%), autoimmune hepatitis (18.3%), other viruses (7.3%), mushroom toxicity (6.0%), Wilson's disease (5.5 %), arterial thrombosis or Budd-Chiari syndrome (6.8 %), and various other causes (*i.e.*, acute alcoholic or post-traumatic). In 363 analysable ALFT cases (60.5%), all clinical aetiologies were eliminated and these cases were considered as clinically unexplained.

Of these 363 clinically unexplained cases, in 62 (10.7% of analysable ALFT) no drug exposure was found within 30 days before index date (ID, date of the onset of the liver disease). Of the 301 cases where a drug exposure within 30 days of symptom onset had been recorded, 114 (19.6% of analysable ALFT) ALFT was attributed to acute drug overdose; 187 (32.1% of analysable ALFT) non-overdose cases were exposed to a drug within 30 days before ID: 40 to at least one NSAID, and 147 to drugs other than NSAID. Two-thirds were female, mean age was around 40 years, and over 81% were ultimately transplanted. Forty cases were exposed to a total of 43 NSAID within 30 days before ID. Thirty-five (87.5 %) of the 40 cases exposed to NSAID were also exposed to other drugs, including paracetamol in 22 (55.0 %). Of the 147 non-NSAID and non-overdose cases, 59 (40.1 %) were exposed to non-overdose paracetamol within 30 days before ID, and 81 (43.0%) of all 187 non-overdose cases.

One hundred eleven (97.4%) of the 114 overdoses were attributed to paracetamol.

The overall NSAID event rate was 1.59 (95%CI 1.14-2.17) ALFT cases per million treatment-years, corresponding to 4.37 cases per billion DDD, with no significant difference between individual NSAID. The common NSAIDs celecoxib, diclofenac, ibuprofen, ketoprofen, naproxen and nimesulide all had point estimates below 10 per million treatment-years or billion DDD, and an upper limit of the 95%CI below 5 per million treatment-years, except for naproxen (5.89) and celecoxib (7.79).

Event rates for all NSAIDs pooled were almost four times higher in Ireland than in all countries pooled.

Over the same period, 192 cases were exposed to paracetamol within 30 days before ID, 81 of which without overdose, resulting in ALFT rates of 3.31 (95%CI 2.63-4.11) per million treatment-years for non-overdose paracetamol and 7.84 (95%CI 6.77-9.04) per million treatment-years when overdoses were included. Confidence intervals did not overlap with those of event rates for all NSAIDs pooled.

These results remained consistent over the sensitivity analyses, such as increasing the exposure window to 90 days, or reducing it to 15 or 7 days, or removing NSAID-exposed

cases also exposed to paracetamol, or including cases with paracetamol overdose that were also exposed to NSAIDs. (13)

This first SALT study will be completed by a second similar study (SALT-II), described here below, that will cover in a similar fashion the years 2008-2013, in the five main countries contributing to SALT-I.

The main objective of SALT-I concerned only the risks associated with NSAIDs. One of the main objectives of the SALT-II study is to assess the risks associated with other drugs than NSAID. The incidence of these very severe drug-induced acute liver failure is very low: we could identify only 40 cases associated with NSAIDs over 2005-2007, and fewer still with other drugs except paracetamol. To improve the precision of the measures of incidence, and to be able to identify emergent risks, it would seem desirable to increase the number of cases identified, by continuing the study for the next six years (2008-2013), and studying the possibility of expanding the network to other countries (Germany, Spain, Nordic or Eastern European countries).

The products of interest of the SALT-II study will thus be all drugs including herbal medicines.

5 STUDY OBJECTIVES

The primary objective is to estimate the risk of drug-exposed ALFT in adults, according to the population exposure to the same drugs.

Secondary objectives are:

- To compare event rates between countries, for all drugs and for specific drugs,
- To compare the effect of choosing different denominators (number of subjects, person-time, DDD) on the relative frequencies measured, and to measure the impact of choice of the exposure window of 7 to 90 days on the observed frequencies.

6 METHODS

6.1 GENERAL STUDY DESIGN

This is a multicentre, multinational retrospective case-population study of drug-exposed patients of ALFT.

As in the SALT-I study, the cases will be abstracted from participating liver transplant units, after identification from national/local transplant registries, in five European countries: France, Ireland, Italy, the Netherlands and the UK.

All patients registered for liver transplantation over a six-year period (01/01/2008 – 31/12/2013) will be identified.

Case selection will be done in the same three-step way as of SALT-I: in the first step, patients with ALF and with other than ALF diagnoses (chronic liver failure, CLF) will be identified, for which succinct demographic data will be collected. In the second step, patients with ALFT will be classified into those with (*i.e.* viral hepatitis, auto-immune hepatitis, etc.) or without identified clinical cause. In the third step of case selection, ALFT patients without identified clinical cause will be sorted into acute drug overdose (with or without suicidal intent); exposed to drugs 30 days prior to ID; not exposed to drugs. For drug-exposed cases of ALFT, full information on drug use will be extracted (including for herbal medicines).

Data collection will be performed for the 90-day exposure window.

The National Case Selection Committee Hepatologist (NCSCH) will validate the data at each step of case selection confirming the clinical and laboratory case definition criteria. The NCSCH will also validate the ID (date of onset of liver disease). The CRA appointed for data collection in the transplant centres will anonymize and scan medical records to fill out the case report form (CRF).

The case selection flow chart is described in Appendix II and in Section 7.3.

The comparator will be population-based: if possible, drug utilisation populations adjusted for age and sex will be determined from overall country-wide sales of all or certain drugs identified in SALT-I, and from utilisation patterns from existing databases or ad hoc studies in the case source population, depending on data availability.

6.2 PARTICIPATING COUNTRIES AND CENTERS

The SALT-I study identified very few or no drug-exposed cases of ALFT in Greece and Portugal; it is therefore proposed that SALT-II be restricted initially to the five main contributors to SALT-I: France, Ireland, Italy, the Netherlands, and the UK.

If needed to improve representativeness or increase the power of the study, it could be extended to Spain, which already has an active network of drug-induced injury centres, to Germany, the largest European country in population size, to the Nordic countries and to Eastern European countries.

6.3 PERIOD

All patients registered for liver transplantation over a six-year period (01/01/2008 – 31/12/2013) will be identified.

6.4 CASES

6.4.1 CASE DEFINITION

The cases fulfilling the following eligibility criteria will be considered for data collection: (11)

- Adult patients of ≥18 years of age at the time of registration on the transplantation list,
- Patient registered on the transplantation list between 1st January 2008 and 31st December 2013, whether the transplantation is actually performed or not,
- Patients who are residents of the country where they were registered.

The non-eligibility criteria will be:

- Patients <18 years of age at the time of registration on the transplantation list,
- Patients not resident in the selected countries.

6.4.2 CASE IDENTIFICATION

All patients registered for liver transplantation for any reason at eligible centres within the study period were identified through either national (France: CRISTAL; Ireland and UK: UK Transplant Registry; Netherlands: National Waiting List;) or local transplant lists (Italy).

Criteria for several registrations on the transplant list will be as follows:

1) If the case was registered on the transplantation list several times with the first registration due to ALF, the first registration will be taken and the following registrations will be noted;

2) If the case was registered on the transplantation list several times with the first registration due to CLF and any of the following due to ALF, the first registration for ALF will be taken and the first registration will be noted;

3) If the case was registered on the transplantation list several times due to CLF at each time, the first registration will be taken and the following registrations will be noted;

4) If the case was registered on the transplant list before 01/01/2008 and re-registered another time within the study period, the registration within the study period (considering the rules above) will be taken, and the registration before 2008 will be noted.

6.4.3 CASE SELECTION

The case selection is a three-step process, done by the National Case Selection Committees (Appendix II):

The first step of case selection will identify patients with ALF and those with diagnoses other than ALF (chronic liver failure, CLF), for which succinct demographic data will be collected (CRF-1, Appendix III).

In the second step, patients with ALFT will be separated into those with (*i.e.* viral hepatitis, auto-immune hepatitis, etc.) or without an identified clinical cause. Patients with an identified clinical cause will not be further assessed for drug exposure (CRF-2, Appendix III). In the third step, for ALFT patients without an identified clinical cause, all information on drug use will be documented under the control of the NCSCH (CRF-3, Appendix III). The NCSCH will classify these cases into

- cases with acute drug overdose (with or without suicidal intent),
- cases exposed to drugs 30 days prior to ID,
- cases not exposed to drugs.

and will determine for each one the ID (date of the onset of the liver disease) and transmit his conclusions to the study coordinating centre. (11)

6.4.4 CASE CONFIRMATION

The NCSCH will validate the data, confirming the clinical and laboratory case definition criteria. (11)

6.4.5 INDEX DATE AND EXPOSURE

The index date (ID) is the date of onset of liver disease: date of initial symptoms or date of laboratory evidence such as elevation of liver enzymes or date of encephalopathy. These dates will be determined and validated by the NCSCH.

For all drugs, including herbal medicines, the exposure window selected is within 30 days prior to ID. The 30-day time window was chosen with reference to the reference causality method for drug-related hepatotoxicity based on international consensus conferences. (5, 14-16) Other exposure windows (90, 15 and 7 days) will be used for sensitivity analyses. (11)

6.4.6 DATA ELEMENTS FOR CASES

Three different datasets will be generated for subjects registered in the transplant waiting list, one at each step of the case validation process. CRF-1 CRF-2, and CRF-3 will be completed by CRA and validated by the local physician of the transplant centre.

6.4.6.1 CRF-1: All patients registered for liver transplantation

Data collected on CRF-1 constitutes the basis for the first step of case selection, *i.e.* for separating ALF from non-acute liver failure. CRF-1 will be the only set of data collected for patients rejected at the first step such as patients with non-acute liver failure (CLF) and will be validated by the NCSCH.

CRF-1 will be also accompanied by the scanned documentation of liver biopsy / histology in local language (CRF-1, Appendix III). CRF-1 will record some demographic and clinical data such as:

- Age, sex,
- Date of registration on the liver transplant list,
- Indication for transplantation (diagnosis),
- Other parameters…

6.4.6.2 CRF-2: Patients registered for ALF

In addition to CRF-1, the elements that prove ALF diagnosis and that enable ascertainment of a specific clinical cause for ALF will be recorded (CRF-2, Appendix III), such as:

- Viral hepatitis (HAV, HBV, HCV, HEV, CMV, EBV, HSV, others),
- Autoimmune hepatitis,
- Other causes (liver ischemia, Wilson's disease, toxic non-drug [i.e. mushrooms, CCL4]),
- Alcohol consumption.

CRF-2 will be also accompanied by the scanned documentation of the relevant clinical raw data in the local language.

6.4.6.3 CRF-3: Patients with ALFT without defined clinical cause:

The patients that do not have a documented clinical cause for ALFT will be assessed with a more complete dataset defined in CRF-3 (CRF-3, Appendix III).

For each drug, the following information will be recorded:

- Information on drug use (for each drug recorded; name, dose / day, route of administration, indication, start and stop dates),
- Information on drug overdose (name, amount, drug analysis in blood if available),
- Information on possible prechallenge history (name, if the drug is associated with a liver failure).

CRF-3 will be also accompanied by the scanned documentation of the relevant clinical raw data in the local language.

6.4.7 NUMBER OF CASES EXPECTED

The number of subjects included in the study is estimated from the results of the SALT-I study. (13)

The SALT-I study identified 363 drug-exposed cases of ALFT in the seven participating countries over the three-year study period, out of 600 cases of ALFT. There were very few or no drug-exposed cases of ALFT in Greece & Portugal; it is therefore proposed that SALT-II be restricted initially to the five main contributors to SALT-I: France, Ireland, Italy, the Netherlands, and the UK. Over the six years of SALT-II, it is expected that 1200 all-cause ALFT and 726 drug-associated ALFT will be identified, so that total numbers would reach 1800 ALFT and over 1000 drug-associated ALFT.

If needed to improve representativeness or increase the power of the study, it could be extended to Spain, which already has an active network of drug-induced injury centres, to Germany, the largest European country in population size, to the Nordic countries and to Eastern European countries. Doubling the population base would double the number of cases, if the transplant activity is homogeneous over Europe.

6.4.8 CAUSALITY ASSESSMENT

Causality assessment was the secondary objective of SALT-I. The performance and usefulness of different causality methods were explored by a pilot study; its consensus points were applied to the main SALT-I: 1) having full data on drugs including International Non-Propriety Name (INN) and doses except for NSAIDs; 2) using the WHO causality scale, 3)

applying the case circuit among the experts simulated in the pilot study. Collected data in SALT-I were mostly the same for all drugs, and the experts were blinded to the names of the NSAIDs, they were all judged as having possible causality.

As a conclusion, causality assessments in SALT-I found that this was not indeed contributive to differential evaluation of drugs. The final causality was driven by previous knowledge of possible hepatotoxicity, which was not helpful to identify or quantify possible new risks. (17)

Because the causality assessment results of the SALT-I were not indeed contributive, this will not be done in the SALT-II.

6.4.9 ADVERSE EVENT REPORTING

Since the study is a non-interventional study, which is based on secondary use of data, the reporting of suspected adverse reactions is not required.

6.5 ASSESSMENT PARAMETERS

Parameter definition is the incidence rate of ALFT.

- The numerator of the incidence rate is the number of cases of ALFT where the patient has been exposed to the product of interest within 30 days before onset of signs or symptoms of the liver disease.
- The denominator of the incidence rate is the estimated population exposed in the countries where the study is performed according to sales, prescription or dispensation data. Exposure is measured in number of DDD sold over the study period, number of patient-years (number of observed Prescribed Daily Doses sold over a year), and if available from population databases, the number of patients treated over the study period.

6.5.1 PRIMARY ENDPOINT

Primary endpoint is the global frequency of occurrence of the ALFT (without clinically defined cause) listed on the transplant list, in subjects exposed to a drug 30 days prior to index date (ID, date of the onset of the liver disease) in five European countries over the 6-year period (2008-2013).

6.5.2 SECONDARY ENDPOINTS

The secondary endpoints are:

- The relative event rates within drugs of the same class,

- Inclusion of data from the SALT-I to determine the overall frequency over nine years (2005-2013),
- Frequency of occurrence measured using different denominators (number of subjects, number of DDD, number of patient-years),
- Frequency based on the number of drug-exposed cases aged between 18 and 70 years (age range observed for subjects transplanted).

6.6 REFERENCE GROUP

6.6.1 REFERENCE POPULATION

The reference populations will be whole country populations. Case rates will be computed with reference to number of users at risk in the general population (per age band, per sex, per concomitant disease or drug usage pattern).
Incidence rates to the general population will then be computed adjusted for these risk factors.

6.6.2 COMPARATOR DATA

6.6.2.1 Drug utilisation patterns:

In all countries, overall and per-drug sales will be obtained from Intercontinental Medical Services, (IMS), or from other available and validated sources, including national health agencies.
Moreover, drug utilisation patterns used to compute number of exposed patients and patient characteristics for stratification or normalization will be obtained from the *Echantillon Généraliste des Bénéficiaires* (EGB) in France. (11, 18, 19) and from similar sources elsewhere.
If possible, usage patterns will then be used to compute exact numbers of patients at risk for each risk factor subgroup. In the case there is a substantial proportion of the drug that is issued over-the-counter (OTC), the usage pattern for that group, if not available from existing data sources, will be extrapolated from studies of OTC usage of NSAIDs (short term use for acute pain or flu or exacerbation of rheumatic disease). (20)

6.6.2.2 Computing numbers of exposed users

From the data elements below one can estimate the total number of patients using the drug, for each of the transplant strata, then the incidence rates for the occurrence of ALFT to

individual drugs. These can then be compared between drugs to evaluate the relative risk ratio for the drugs. OTC users will be considered as short-term users according to existing utilisation studies.

Data of SALT-II will be pooled with data of the previous SALT-I study to estimate the frequency of ALFT identified in nine years (2005-2013). This will allow a greater number of events and a better precision of the risk estimates.

6.6.2.3 Data elements for reference populations

- Number of boxes of drug sold per year
- Numbers of DDD sold
- Mean number of DDD bought by individual patients, per age group, sex and per indication if available
- Number of subjects / users per stratification band. This will be computed after a decision on stratification is made on case specifications, if available.

7 STUDY LOGISTICS

7.1 CONTACTING LIVER TRANSPLANT CENTRES

All 52 liver transplant units in the five countries, identified and considered as eligible in the SALT-I study, will be invited to participate (Appendix I). (11) The contacts and the relative replies will be documented.

7.2 CASE IDENTIFICATION AND INCLUSION

Patients registered on the transplant waiting list will be identified through either national (France: CRISTAL; Ireland and UK: UK Transplant Registry; Netherlands: National Waiting List) or local transplant lists (Italy). CRA(s) from the department, from partner academic organisations or transplant centres, or contracted locally using reputable CRO, who will receive a common training by the Coordinating Centre, will abstract data from the medical files at the participating centres under the supervision of the centre's physician.

For all patients registered on the transplant waiting list between 2008-2013, the CRF-1 will be completed. If the liver transplant centre database contains all necessary information, this will be the only data source for primary purposes. In other cases, the CRA will complete CRF-1 from medical files at the participating centres. CRF-1 will be accompanied by the scanned

documentation of liver biopsy / histology in local language. For all ALFT patients (validated by the centre's physician), CRF-2 will be completed by CRA from medical files at the participating centre. CRF-2 will be accompanied by the documentation of the relevant clinical raw data in the local language. For all ALFT patients without identified clinical cause (validated by the centre's physician), CRF-3 will be completed by CRA from medical files at the participating centre. CRF-3 will be accompanied by a copy of the relevant clinical raw data in the local language.

All necessary source data will be anonymized and scanned on site, or photocopied and scanned at the Coordinating Centre. The data will be input to the database onsite if possible or at the Coordinating Centre using scanned data.

Patient information will be assessed based on the information recorded at the time of registration at the transplant centre, whether the transplant occurs or not.

7.3 CASE SELECTION AND CONFIRMATION

The NCSCH will validate the cases, confirming the clinical and laboratory case definition criteria.

At the first step of case selection, where ALFT cases will be separated from CLF, a CRA will prepare all documents necessary for the hepatologist (CRF-1 and scanned anonymized data) who transmits his conclusions to the Coordinating Centre. A brief documentation of the case, which contains the essential data to conclude, may be prepared by the Coordinating Centre staff and sent to the NCSCH in order to minimise the workload of the NCSCH. If the liver transplant centre database has all necessary information, the hepatologist will review only ALFT patients and cases not clearly defined as CLF.

At the second step of case selection, where ALFT cases will be classified into ALFT with or without clearly identified clinical cause, a CRA will prepare all documents necessary for the hepatologist (CRF-2 and scanned anonymized data) who transmits his conclusions to the Coordinating Centre. A brief documentation of the case, which contains the essential data to conclude, could be prepared by the Coordinating Centre staff and sent to the NCSCH in order to minimise the workload of the NCSCH.

Finally, the NCSCH will review all ALFT cases without identified clinical cause to classify into cases with acute drug overdose (with or without suicidal intent), or cases exposed to drugs 30 days prior to ID, or cases not exposed to drugs. The NCSCH will determine the ID (date of the onset of the liver disease). A CRA will prepare all documents necessary for the

hepatologist (CRF-3 and scanned anonymized data) who transmits his conclusions to the Coordinating Centre. A brief documentation of the case, which contains the essential data to conclude, could be prepared by the Coordinating Centre staff and sent to the NCSCH in order to minimise the workload of the NCSCH.

7.4 QUALITY CONTROL

A random set of the abstracted data will be verified for quality and completeness of abstraction by an independent quality control (QC) team, comparing abstracts with original data on site or from scanned data.

8 DATA MANAGEMENT

A specific database will be developed for this study, using standard tools (Filemaker Pro, SQL+, MySQL, Grails …), allowing for deported (eCRF) or remote (iCRF) input.
This database will be tested before data input. Database access will be restricted to authorized personnel, using state-of-the-art security techniques.
The database will be located and managed by the coordinating centre.
This will be completed when the assessment details are defined.
A Data Review Plan will be developed to ensure the quality of the data and data checks will be programmed on SAS® software.

9 STATISTICAL ANALYSIS

A detailed Statistical Analysis Plan (SAP) will be developed and filed before database lock. Statistical analyses will be carried out using SAS® software (SAS Institute, North Carolina, USA, current version), following the analysis plan.

9.1 MAIN ANALYSIS

- Descriptive analysis: A descriptive analysis of all drug-exposed cases of ALFT will be performed.
- Rate estimations per country: Per country rates of drug-exposed transplantation registered ALF will be computed as the ratio of the number of cases identified in the country to the population exposure. Population exposure will be measured in treatment-years (source: IMS). The estimation of the rate of drug-exposed ALFT cases within 30 days prior to ID, with a 95% CI from a Poisson distribution, expressed in

cases per million treatment-years. The frequency of ALFT will be calculated also for people aged 18 to 70 years.

- Pooling: Data of SALT-II will be pooled with data of the previous SALT-I study to estimate the frequency of ALFT identified in nine years (2005-2013). This will allow a greater number of events and a better precision of the risk estimates.

9.2 SENSITIVITY ANALYSIS

Sensitivity analyses will be performed using different sources of information to determine the size of populations at risk, based on sales data (provided by IMS), dispensation and reimbursement data, (CNAM-TS Medicam data for France or equivalent in the other participating countries) and usage data determined from the information about the actual or theoretical use of products: for DDD (primary analysis) as defined by the WHO Nordic collaborating centre on drug statistics methodology, or depending on usage patterns identified by reimbursement (France), or the basis of population data (*i.e.* Italy, the Netherlands, the UK), taking as denominator the total consumption in DDD, in patient-years (PDD/365), or patient numbers (based on patterns of use). The study will not be limited to NSAID but will include all drugs families found present in at least five cases.

Sensitivity analyses will be performed for different exposure windows of interest (from 7 to 90 days).

10 STRENGTHS AND LIMITATIONS

The strengths of the study are:

- To focus on drug-associated ALFT, whether the patient is transplanted or not,
- Exhaustive participation of liver transplant centres in Europe, which provides the inclusion of the target cases (ALFT), per-country identification of cases can therefore be complete which is a prerequisite for a case-population approach,
- Case-population design, which is appropriate for very rare easily identifiable outcomes for all cases exposed and compared to use of drugs in a defined area (country, region),
- To give an estimate of absolute population-based event rates,
- To give estimations independent of causality assessments or spontaneous reporting,
- To expand the network of drug-exposed liver injury leading to transplantation (developed by the SALT-I study) for another six-year period for a total of nine years, and evaluate all drugs concerned other drugs,

- To provide results necessary for planning a prospective phase.

The limitations of the study are:

- Retrospective design because it depends on existing data, the nature and the quality of which may vary,
- Lack of systematic drug exposure data, because recorded drug exposure may be dependent on causality evaluation of treating physician,
- Complexity of accurately estimating population drug exposure data,
- Lack of information about the possible concomitant risk factors other than basic items such as age and gender, limiting the possibility of identifying the putative high-risk groups.

11 REGULATORY ASPECTS

The final protocol will be submitted to the Competent Authorities according to the local regulatory requirements.

11.1 CONTRACTS

Financing of the study will be obtained through Bordeaux University Foundation (BUF) that receives donations from pharmaceutical companies. The BUF authorises ADERA and the Bordeaux University to sign individual contracts with the committees and the centres. These will be submitted to regulatory authorities as required by local regulations.

11.2 PROTECTION OF HUMAN SUBJECTS

In France, the SALT-I study was submitted to the Committee for the Protection of Persons for the Southwest and Overseas III (*Comité de Protection des Personnes, Sud-Ouest et Outre Mer III, CPP– SOOM III*), which examined the relevance of the project and the qualifications of the investigator, but also that the subjects received sufficient information on risks and benefits of the study to be performed. The CPP concluded that they did not need to examine the SALT-I study, as it was a non-interventional. Since SALT-II is the continuation and the prolongation of the SALT-I with the same methodology, it was not necessary to (re)submit the SALT-II to the CPP.

11.3 DATA PROTECTION

The study protocol has been approved by the *Commission Nationale de l'Informatique et des Libertés* (CNIL) in France, and will be submitted to the relevant bodies in the other participating countries. The Steering Committee members will follow the scientific conduct of the study.

All Steering Committee members and all study personal are obliged to maintain medical confidentiality concerning any identifiable patient data.

The patients will be identified with an ID code and the same will be done for the sites. A list of the patients and their relative ID codes will be filed at each site.

12 RESPONSIBILITIES OF THE PARTIES

Financing of the study has been obtained through BUF, which has received donations from pharmaceutical industries.

BUF has delegated the Department of Pharmacology (coordinating centre) for the conduct and the management of the study. The study protocol is developed by the coordinating centre in Bordeaux, Department of Pharmacology. Since the methodology follows the same of the SALT-I study, the protocol of SALT-II has been internally approved without any requirements from the BUF or donators, and submitted to the relevant authorities in France.

The coordinating centre assists and supports the Steering Committee and follows its indications to conduct the study, write the final study report, and archive the data according to regulatory obligations. It is the guarantor of the study. It ensures that national and European regulations are respected, as well as Good Pharmacoepidemiology Practices as described by ISPE (www.pharmacoepi.org) and ENCePP Code of Conduct and methodological standards guide. The ENCePP seal will be sought for. Study protocol and results will also be made public according to ENCePP requirements.

The Steering Committee reviews and provides input on the scientific quality of the project, data analysis, and orientates publications. It may also have to give advice pertaining to any situation that could interfere directly or indirectly with the study. The Steering Committee may name a publication committee that is responsible to prepare the final report of the study, scientific articles and the abstracts in collaboration with the Coordinating Centre.

The National Case Selection Hepatologist will be designated in each participating country, and is responsible to follow the case selection flow chart and validate and classify the ALFT cases. CRA collects original data in various transplant centres, scans the anonymized original

raw data, and classify the cases in different steps. Each NCSCH and the CRA will select the cases by their country at step 1, 2 and step 3, documenting for each case the criteria reasons for rejecting the case if the case is not moved to the next step and will validate the relevant CRFs.

The authorship of the publications will be defined after finalisation of the protocol. The sequence of authors is to be decided on the basis of the contribution of the members. In case of several publications, author sequence to be decided on by the project group together with the publication committee.

13 PROVISIONAL STUDY CALENDAR

Regulatory Submissions:	CCTIRS approval for France received on 8th July 2013. CNIL approval for France received on 11th July 2013. CCTIRS and CNIL will be informed about the amended version of the study protocol.
Study set-up:	1st semester of 2014
Data collection:	1st semester of 2014 – 4th quarter of 2014
Data analysis:	4th quarter of 2014 – 1st quarter of 2015
Final report:	1st quarter of 2015 – 2nd quarter of 2015

14 FUTURE AMENDMENTS AND DEVIATIONS

If necessary, any substantial amendment and update to the study protocol after the start of data collection, including a justification for each amendment or update, dates of each change and a reference to these sections of the protocol where the change has been made will be prepared. Necessary bodies and ENCePP will be informed without delay.

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16 APPENDIX I: LIVER TRANSPLANT CENTRES

16.1 FRANCE

City / Inter Rég	Contact details
BESANCON / DIJON	CHU Besançon - Hôpital Jean Minjoz - Chateaufarine Chirurgie Digestive Pr Mantion 3 Boulevard Alexandre Fleming 25030 Besançon Cedex CHU Dijon - Hôpital du Bocage Service Hépato-Gastroentérologie du Pr HILLON 2 bd Maréchal-de-Lattre-de-Tassigny - BP 77908 21079 Dijon Cedex
BORDEAUX	CHU Bordeaux- Hôpital Saint-André Service de Chirurgie viscérale et transplantation hépatique 1 rue Jean Burguet 33075 Bordeaux Cedex CHU Bordeaux - Pellegrin Transplantation Hépatique 5ème étage - Tripode Place Amélie Raba Léon 33076 Bordeaux Cedex
CAEN	CHU Caen – Hôpital Côte de Nacre Chirurgie Digestive Avenue de la Côte de Nacre 14033 Caen Cedex 5
CLERMONT FERRAND	CHU Clermont Ferrand – Hôpital Estaing Chirurgie Digestive 1 Place Lucie Aubrac 63003 Clermont-Ferrand Cedex 1
CLICHY	AP-HP - Hôpital Beaujon Chirurgie Digestive 100 Boulevard du Général Leclerc 92118 Clichy Cedex
CRETEIL	AP-HP - Hôpital Henri Mondor Chirurgie Digestive 51 Avenue de Lattre de Tassigny 94010 Créteil Cedex
GRENOBLE	CHU Grenoble – Hôpital A. Michallon Chirurgie Digestive 12ème étage Boulevard de la Chantourne - BP 217 38043 Grenoble Cedex 9
LILLE	CHRU Lille - Hôpital Claude Huriez Chirurgie Digestive 1 place de Verdun 59037 Lille Cedex
LIMOGES	CHU Limoges - Hôpital Dupuytren Chirurgie Digestive 2 av Martin Luther King 87042 Limoges Cedex 1

LYON 3ème	CHU Lyon - Hôpital Edouard Herriot Chirurgie Digestive - Pavillon D3 5 place D'Arsonval 69437 Lyon Cedex 03
LYON 4ème	CHU Lyon - Hôpital de la Croix-Rousse Chirurgie générale et digestive et de la transplantation hépatique et intestinale 103 Grande Rue de la Croix-Rousse 69317 Lyon Cedex 04
MARSEILLE	AP-HM - Hôpital de la Conception Chirurgie digestive 147 Boulevard Baille 13385 Marseille Cedex 05
MONTPELLIER	CHU Montpellier - Hôpital Saint-Eloi Chirurgie Digestive C 80 Av Augustin Fliche 34295 Montpellier Cedex 5
NICE	CHU Nice - Hôpital de L'Archet Centre de Transplantation Hépatique 151 route Saint-Antoine de Ginestière - BP 79 06202 Nice Cedex 3
PARIS 12EME	AP-HP - Hôpital Saint-Antoine Chirurgie Hépato-Biliaire et Transplantation Hépatique 184 rue du Faubourg Saint-Antoine 75012 Paris 12ème
PARIS 13EME	AP-HP - Groupe Hospitalier Pitié-Salpêtrière Chirurgie Digestive et Hépato-Bilio-Pancréatique Bâtiment Montyon 47 Boulevard de L'Hôpital 75013 Paris 13ème
PARIS 14EME	AP-HP - Hôpital Cochin Chirurgie Digestive Hépato Biliaire Endocrinienne 27 rue du Faubourg Saint-Jacques 75014 Paris 14ème
RENNES	CHU Rennes - Hôpital Pontchaillou Service de chirurgie hépatobiliaire et digestive 2 rue Henri Le Guilloux 35033 Rennes Cedex 9
STRASBOURG	CHU Strasbourg – Hôpital de Hautepierre Chirurgie Générale, Hépatique, Endocrinienne et Transplantation Avenue Molière 67098 Strasbourg Cedex 2
TOULOUSE	CHU Toulouse - Hôpital Rangueil Chirurgie Générale et Digestive Bâtiment H2 – 5ème étage 1 av Jean Poulhès TSA 50032 31059 Toulouse cedex 9
VILLEJUIF	AP-HP - Hôpital Paul-Brousse Service Hépato-Biliaire 12-14 avenue Paul-Vaillant-Couturier BP 200 94804 Villejuif Cedex

16.2 ITALY

City	Contact details
ANCONA	Presidio Ospedaliero Umberto I Chirurgia Epatica e dei Trapianti di Fegato, Rene, Pancreas Via Conca 71 60100 Cigliano (VC)
BARI	Azienda Ospedaliero-Universitaria Consorziale Policlinico di Bari Dipartimiento Emergenza Trapianto di Organi Piazza Giulio Cesare 11 70124 Bari
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BOLOGNA	Policlinico S.Orsola-Malpighi Chirurgia Generale e dei Trapianti - Pinna Via Massarenti 9 40138 Bologna
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MILANO MAGGIORE	Ospedale Maggiore Policlinico Unità Operativa di Chirurgia Generale e dei Trapianti di Fegato IRCCS Ospedale Maggiore Policlinico Via Francesco Sforza 35 20122 Milano
MODENA	Azienda Ospedaliera – Universitaria Policlinico di Modena Emilia Romagna Dipartimiento A.I.n. 2 Chirurgia Generale e Specialità Chirurgiche Chirurgia dei Trapianti Via del Pozzo 71 41124 Modena
NAPOLI	Azienda Ospedaliera "A. Cardarelli" Dipartimiento dei Trapianti UOSC Trapianto Fegato Via A. Cardarelli 9 80131 Napoli

PADOVA	Azienda Ospedaliera di Padova Unità Operativa di Chirurgia Epatobiliare e Trapianti Epatici Policlinico Universitario, 3° piano Via Giustiniani 2 35128 Padova
PALERMO	ISMETT Chirurgia Addominale e dei Trapianti Via Ernesto Tricomi 5 90127 Palermo
PISA	Azienda Ospedaliero-Universitaria Pisana Unità Operativa Trapiantologia Epatica Universitaria Via Zamenhof 1 56100 Pisa
ROMA SAN CAMILLO	Azienda Ospedaliera San Camillo - Forlanini Dipartimento Interaziendale di Chirurgia dei Trapianti Centro “Silvio Natoli” U.O.C. Chirurgia generale e dei Trapianti d’Organo Ospedale INMI “L.Spallanzani’’ Via Portuense 292 00149 Roma
ROMA GEMELLI	Policlinico Universitario A. Gemelli UOC Chirurgia Generale e Trapianti d’Organo Largo Agostino Gemelli 8 00168 Roma
ROMA	Policlinico Umberto I di Roma U.O.C. Chirurgia Gastroentererologica Epato-Biliare Viale del Policlinico 155 00161 Roma
ROMA S. EUGENIO	Ospedale S. Eugenio Chirurgia Generale e Trapianti Piazzale dell’Umanesimo 10 00144 Roma
TORINO	A.O.U. San Giovanni Battista di Torino Centro Trapianto di Fegato Corso Bramante 88 10126 Torino
UDINE	Azienda Ospedalier-Universitaria “Santa Maria della Misericordia” Clinica Chirurgica Centro Trapianti Piazzale Santa Maria della Misericordia 15 33100 Udine
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16.3 IRELAND

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16.4 THE NETHERLANDS

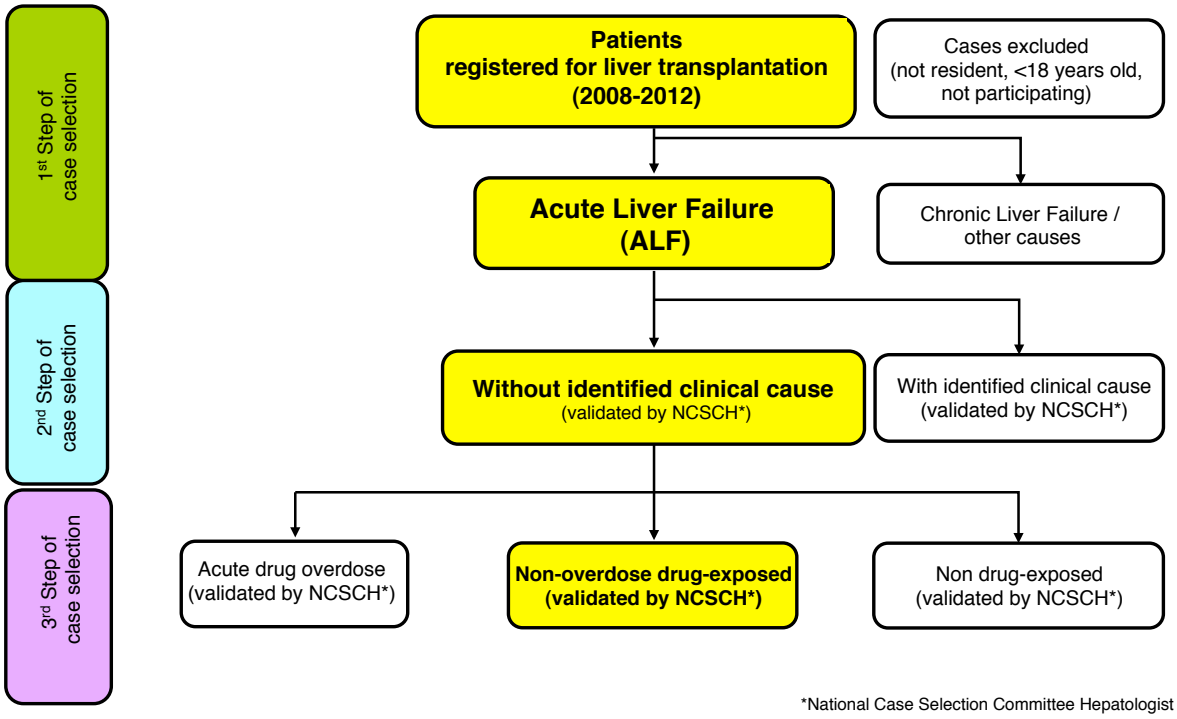
City	Contact details
GRONINGEN	Universitair Medisch Centrum Groningen Hepatobiliaire Chirurgie & Levertransplantatie Huispostcode BA33 Postbus 30001 9700 RB Groningen
LEIDEN	Leids Universitair Medisch Centrum (LUMC) Albinusdreef 2 Postbus 9600 2333 ZA Leiden
ROTTERDAM	Erasmus MC 's Gravendijkwal 230 3015 GD Rotterdam Postbus 2040 3000 CA Rotterdam

16.5 THE UNITED KINGDOM

City	Contact details
BIRMINGHAM	Queen Elizabeth Hospital Liver unit Birmingham B15 2TH
CAMBRIDGE	Cambridge University Hospitals NHS Foundation Trust Addenbrooke's Hospital Hills Rd Cambridge CB2 0QQ
EDINBURGH	Lothian Universities Hospital Trust Royal Infirmary of Edinburgh Scottish Liver Transplant Unit 51 Little France Crescent Edinburgh EH16 4SA Scotland
LEEDS	St James's University Hospital Liver Unit Beckett Street Leeds LS9 7TF
LONDON	The Royal Free Hospital Hepatology department Pond Street London NW3 2QG
LONDON	King’s College Hospital Liver Transplant Office Denmark Hill London SE5 9RS
NEWCASTLE	The Freeman Hospital Department of Hepatobiliary and Transplant Surgery High Heaton Newcastle upon Tyne NE7 7DN

17 APPENDIX II: CASE SELECTION FLOWCHART

The first three steps of the case selection process will be performed by the NCSCH for each country.



18 APPENDIX III: CRF

Pharmacologie médicale

Pharmaco-épidémiologie
CIC Bordeaux CIC1401

SALT-II

Study of Acute Liver Transplant

« Prolongation and continuation of the SALT-I study »

A study of drug-exposed acute liver failure
in European transplant centres

Case Report Form - CRF

Version: 3.0
4th March 2014

Completing date	|___|___| |___|___| 201|___|
Completed by	|___|___|___|___|___|___|___|___|___|___|___|___|___|
Patient ID code	2 - |___|___| - |___|___| - |___|___|___|___|
Patient Initials	|___| (First name) |___| (Surname)

CENTRE COORDINATEUR
Service de Pharmacologie, Pharmaco-épidémiologie CIC Bordeaux CIC1401
INSERM - Université de BORDEAUX – CHU de Bordeaux – Adera
Bâtiment Le Tondu – case 41
146 rue Léo Saignat – 33076 Bordeaux Cedex

SALT-II – CRF/ Part I

TO BE COMPLETED FOR ALL PATIENTS REGISTERED FOR LIVER TRANSPLANTATION

1. General informations

1.1. Patient ID Code	|___|___| - |___|___| - |___|___|___|___| Barcode	
1.2. Patient initials	|___| Name |___| Surname	
1.3. Date of file created	|___|___| / 20|___|___| Month Year	
1.4. Date of birth	|___|___| / |___|___|___|___| Month Year PATIENT SHOULD BE **AT LEAST 18 YEARS OLD** AT THE TIME OF REGISTRATION ON TRANSPLANT LIST	❑ ND
1.5. Region (current)	|___|___|___|___|___|___|___|___|___|	❑ ND
1.6. City (current)	|___|___|___|___|___|___|___|___|___|	❑ ND
1.7. Sex	❑ Male ❑ Female	❑ ND
1.8. Resident in the country	❑ Yes ❑ No IF NO, **PART II SHOULD NOT BE COMPLETED**	❑ ND

2. Transplantation information

2.1. Date of registration in transplant list	|___|___| / |___|___| / 20|___|___| Day Month Year ONLY CASES **BETWEEN 2008 AND 2013** ENTER IN THE STUDY	❑ ND

2.2. Indication of transplantation (diagnosis) (as reported in the clinical record) ❑ ND

|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

2.3. Cause of indication for liver transplantation

❑ Acute liver failure ❑ Chronic liver failure (or other causes) ❑ ND

IF INDICATION IS CHRONIC LIVER FAILURE (OR OTHER CAUSES), **PART II SHOULD NOT BE COMPLETED**

2.4. Proven by native liver histopathology	❑ Yes	❑ No	❑ ND
If yes, date of **native** liver histopathology	|___|___| / |___|___| / 20|___|___| Day Month Year		❑ ND
2.5. Transplanted	❑ Yes	❑ No	❑ ND

3. Scanned copy of native liver histopathology

	Yes	No	ND
3.1. Available	❑	❑	❑
3.2. Attached to CRF	❑	❑	❑

Patient Initials: |__| / |__| ID: 2 - |__|__| - |__|__| - |__|__|__|__|

SALT-II – CRF/ Part II

TO BE COMPLETED FOR ALL PATIENTS REGISTERED TO A TRANSPLANTATION LIST FOR ALF (IN ADDITION TO CRF/PARTI)

CAUSE OF ACUTE LIVER FAILURE

DATE BEFORE TRANSPLANTATION AND THE CLOSEST TO REGISTRATION

1. Viral hepatitis	❑ Yes	❑ No	❑ ND
If yes, please specify the virus	|__|__|__|__|__|__|__|__|__|__|__|__|__|		❑ ND
2. Autoimmune disease			
Acute autoimmune hepatitis	❑ Yes	❑ No	❑ ND
Other autoimmune disease	❑ Yes	❑ No	❑ ND
If yes, please specify the disease	|__|__|__|__|__|__|__|__|__|__|__|__|__|		❑ ND
3. Other causes			
Liver ischemia	❑ Yes	❑ No	❑ ND
Wilson's disease	❑ Yes	❑ No	❑ ND
Other cause	❑ Yes	❑ No	❑ ND
If yes, please specify	|__|__|__|__|__|__|__|__|__|__|__|__|__|		❑ ND
4. HIV	❑ Yes	❑ No	❑ ND
5. Alcohol consumption	❑ Yes	❑ No	❑ ND
If yes, specify the quantity as written in the patient file	|__|__|__|__|__|	❑ ND	

6. Conclusion on the ALFT case

❑ ALFT with defined clinical cause ❑ ALFT without defined clinical cause

↓

IF CONCLUSION IS ALFT **WITH** DEFINED CLINICAL CAUSE, **PART III SHOULD NOT BE COMPLETED**

SCANNED COPY OF RELEVANT CLINICAL ROW DATA

	Yes	No	ND
Available	❑	❑	❑
Attached to CRF	❑	❑	❑

SALT-II – CRF/ Part III

TO BE COMPLETED FOR ALL DRUG-EXPOSED PATIENTS REGISTERED TO A TRANSPLANTATION LIST FOR ALF WITHOUT DEFINED CLINICAL CAUSE (IN ADDITION TO CRF/PARTI AND CRF/PARTII)

1. OVERDOSE

BEFORE THE TRANSPLANTATION AND THE CLOSEST TO REGISTRATION			
Possible overdose	❑ Yes	❑ No	❑ ND
If yes, date of overdose	|__|__| / |__|__| / 20|__|__|		❑ ND
If yes, name of the drug	|__|__|__|__|__|__|__|__|		❑ ND
If yes, the amount of ingested drug	|__|__|__| |__|__| Quantity Units		❑ ND
If yes, drug analysis in blood	|__|__|__| |__|__| Quantity Units		❑ ND
Suicidal intention	❑ Yes	❑ No	❑ ND

2. PRECHALLENGE

Possible prechallenge history ❑ Yes ❑ No ❑ ND

↳ *If yes,* **Name of the drugs**	**Dose / Day**	**Intake period**	**Liver reaction**
|__|__|__|__|__|__| ❑ ND	|__|__| |__|__| ❑ ND Quantity Units	From |__|__| / |__|__| / 20|__|__| To |__|__| / |__|__| / 20|__|__|	❑ Yes ❑ No ❑ ND
|__|__|__|__|__|__| ❑ ND	|__|__| |__|__| ❑ ND Quantity Units	From |__|__| / |__|__| / 20|__|__| To |__|__| / |__|__| / 20|__|__|	❑ Yes ❑ No ❑ ND
|__|__|__|__|__|__| ❑ ND	|__|__| |__|__| ❑ ND Quantity Units	From |__|__| / |__|__| / 20|__|__| To |__|__| / |__|__| / 20|__|__|	❑ Yes ❑ No ❑ ND
|__|__|__|__|__|__| ❑ ND	|__|__| |__|__| ❑ ND Quantity Units	From |__|__| / |__|__| / 20|__|__| To |__|__| / |__|__| / 20|__|__|	❑ Yes ❑ No ❑ ND

3. DISEASE INFORMATION

BEFORE THE TRANSPLANTATION AND THE CLOSEST TO REGISTRATION			
Date of onset of liver disease	|__|__| / |__|__| / 20|__|__|		❑ ND
Encephalopathy	❑ Yes	❑ No	❑ ND
If yes, date of encephalopathy	|__|__| / |__|__| / 20|__|__|		❑ ND
Date of ALT/AST elevation	|__|__| / |__|__| / 20|__|__|		❑ ND

4. Major medical/surgical events before first symptoms

Major events before first symptoms	❑ Yes	❑ No	❑ ND	
If yes,				
Event	**Period of occurrence**			
|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|	From |___|___| / |___|___| / 20|___|___| To |___|___| / |___|___| / 20|___|___|	❑ ND ❑ ND		
|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|	From |___|___| / |___|___| / 20|___|___| To |___|___| / |___|___| / 20|___|___|	❑ ND ❑ ND		
|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|	From |___|___| / |___|___| / 20|___|___| To |___|___| / |___|___| / 20|___|___|	❑ ND ❑ ND		
|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|	From |___|___| / |___|___| / 20|___|___| To |___|___| / |___|___| / 20|___|___|	❑ ND ❑ ND		

5. Drugs taken within the 3 months before first symptoms

Drugs taken within the 3 months before first symptoms	❑ Yes	❑ No	❑ ND	
If yes,				
Drug name (including anaesthesia & herbal medicine)	**Dose / Day**	**Intake period**	**Chronic treatment** (> 3 months)	**Exposure window**
|___|___|___|___|___|___|___|___|	|___|___||___|___| ❑ ND Quantity Units	From |___|___| / |___|___| / 20|___|___| ❑ ND To |___|___| / |___|___| / 20|___|___| ❑ ND	❑	❑ 90 days ❑ 30 days ❑ 15 days ❑ 7 days
|___|___|___|___|___|___|___|___|	|___|___||___|___| ❑ ND Quantity Units	From |___|___| / |___|___| / 20|___|___| ❑ ND To |___|___| / |___|___| / 20|___|___| ❑ ND	❑	❑ 90 days ❑ 30 days ❑ 15 days ❑ 7 days
|___|___|___|___|___|___|___|___|	|___|___||___|___| ❑ ND Quantity Units	From |___|___| / |___|___| / 20|___|___| ❑ ND To |___|___| / |___|___| / 20|___|___| ❑ ND	❑	❑ 90 days ❑ 30 days ❑ 15 days ❑ 7 days
|___|___|___|___|___|___|___|___|	|___|___||___|___| ❑ ND Quantity Units	From |___|___| / |___|___| / 20|___|___| ❑ ND To |___|___| / |___|___| / 20|___|___| ❑ ND	❑	❑ 90 days ❑ 30 days ❑ 15 days ❑ 7 days

6. Scanned copy of relevant clinical row data

	Yes	No	ND
Available	❑	❑	❑
Attached to CRF	❑	❑	❑