WP6 validation on methods involving an extended audience

Statistical analysis plan / data specifications

The risk of acute liver injury associated with the use of antibiotics. A replication study in the Utrecht Patient Oriented Database

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1. Context

The study described in this protocol is performed within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium). The overall objective of PROTECT is to strengthen the monitoring of the benefit-risk of medicines in Europe. Work package 6 “validation on methods involving an extended audience” aims to test the transferability/feasibility of methods developed in other WPs (in particular WP2 and WP5) in a range of data sources owned or managed by Consortium Partners or members of the Extended Audience.

The specific aims of this study within WP6 are:

- to evaluate the external validity of the study protocol on the risk of acute liver injury associated with the use of antibiotics by replicating the study protocol in another database,
- to study the impact of case validation on the effect estimate for the association between antibiotic exposure and acute liver injury.

Of the selected drug-adverse event pairs selected in PROTECT, this study will concentrate on the association between antibiotic use and acute liver injury. On this topic, two sub-studies are performed: a descriptive/outcome validation study and an association study. The descriptive/outcome validation study has been conducted within the Utrecht Patient Oriented Database (UPOD). Cases of acute liver injury have been identified using hospital discharge diagnoses and/or abnormal laboratory test results related to liver injury. The proposed association study will be performed using UPOD and GP databases.

2. Background

Acute liver injury is one of the most important safety concerns, being the leading cause for drug withdrawal from the market on safety grounds (1). For most suspected hepatotoxic drugs the only existing information comes from spontaneous reports, lacking appropriate risk quantification through formal epidemiological studies (2). A few population-based studies examining the risk of acute and clinically relevant liver injury among users of various drugs have been published, reporting an elevated risk of liver injury in users of antibiotics (3-6). As acute liver injury is often idiosyncratic and because its diagnostic criteria used in epidemiological studies have been variable, the reported range of incidences of acute liver injury caused by antibiotics is broad. In the UK, case-control studies investigating the effect of antibiotics on acute liver injury have generated odds ratios ranging from 94.8 for the combination of amoxicillin/clavulanic acid to 6.2 for tetracyclines (3). Age, sex, alcohol intake, concomitant medication and comorbidities have been proposed as risk factors for antibiotic induced liver injury and may have influenced the quantification of risk estimates (3, 5, 7). In the present protocol, we propose to further quantify the risk of acute liver injury associated with antibiotics in the general population using a case control design in a different primary care database to that in WP2, comparing the results to evaluate the impact of design and population differences on the outcome of the study association.

3. Objectives

In order to meet the WP6 aims mentioned above, we will perform a replication study using the Mondriaan linkage system, in which we want to:

1. estimate the relative risk of acute liver injury associated with antibiotics exposure (users vs non-users),
2. estimate the relative risk of acute liver injury comparing various antibiotics classes,
3. estimate the relative risk of acute liver injury comparing specific individual antibiotics,
4. assess the effect of dose and duration of use for specific individual antibiotics,

Subsequently, the results from the Mondriaan analyses will be compared with the original association study in order to:

- evaluate the external validity of the original study protocol on the risk of acute liver injury associated with the use of antibiotics,
- study the impact of case validation on the effect estimate for the association between antibiotic exposure and acute liver injury.

4. Methods

4.1 Data source

Data will be obtained from the UPOD and Dutch General Practioner databases for which access and linkage will be provided by the Mondriaan project.

Mondriaan project

The Dutch Mondriaan project is a private-public collaboration funded by the Dutch TOP Institute Pharma. Mondriaan is an intermediate organization between researchers and sources of data. Mondriaan does not own data, but has an organizational and technical infrastructure to deliver, and enrich data to researchers. Several data sources can be linked on an individual patient level through a 'trusted third party'. These data sources include pharmacy dispensing data, primary care data, in-hospital data and a number of epidemiological cohorts.The databases within Mondriaan have different starting dates and scope of data. For the present study in-hospital data will be linked to primary care data.

UPOD

UPOD contains information on patient characteristics, laboratory test results, medication orders, hospital discharge diagnoses and medical procedures for all patients treated at the University Medical

Centre Utrecht (UMCU) (8). All available data relate to the hospitalized period only, i.e. out-of-hospital medication data are not captured within UPOD.

Primary care databases: Julius Huisartsen Netwerk (JHN) & Almere Health Care (ZGA)

The ZGA is a GP and pharmacy database, from the Almere region, which covers approximately 200,000 primary care patients. The HNU is a GP database. The LRJG is a GP database with a linkage to additional survey records. Survey information is periodically up-dated through follow-up, including information on a wide range of health and lifestyle related variables. HNU and LRJG merged together into the Julius Huisartsen Netwerk (JHN) and the databases contain routine healthcare data extracted from approximately 200,000 primary care patients in the Utrecht area. Both regions are within the capture area of the UMCU, but the exact overlap is not known.

4.2 Study population

Cases of idiopathic liver injury have been selected from patients aged 18 years or older hospitalized or referred to the UMCU between January 2008 and December 2010. Controls will be sampled from the JHN and the ZGA databases.

4.3 Outcome definition

Patients were initially identified using two algorithms. Algorithm A started from hospital discharge diagnoses, Algorithm B started from lab measurements records.

Algorithm A

- Patients with a (primary or secondary) hospital discharge diagnosis or diagnostic procedure of liver injury (codes listed in appendix 9.1.1).
- Exclusion of patients with a diagnostic code indicating a known other cause of liver injury (cancer, alcoholism, alcohol related problems, gallbladder disease, pancreatic disease, and other chronic liver diseases not included in outcome definition) (codes listed in appendix 9.2.1).

1. Definite cases:

   a) An increase of more than two times the upper limit of the normal range in alanine aminotransferase (ALT>2ULN) (reference values liver related tests UMCU listed in appendix 9.6)

   or

   b) A combined increase in aspartate aminotransferase (AST), alkaline phosphatase (AP) and total bilirubin provided one of them is twice the upper limit of the respective normal range.

2. High ALT cases:
   An increase of more than three times the upper limit of the normal range in alanine aminotransferase (ALT>3ULN)
3. Hy's law cases:
   serum alanine transaminase (ALT) levels > 3 X ULN; and
   bilirubin > 2 X ULN; and
   absence of alkaline phosphatase (AP) elevation.
4. Very high ALT cases:
   An increase of more than ten times the upper limit of the normal range in alanine aminotransferase (ALT>10ULN)

Algorithm B

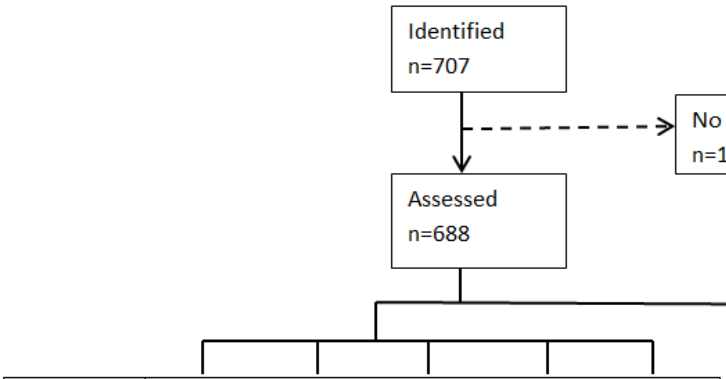
1. Hy's law cases:
   serum alanine transaminase (ALT) levels > 3 X ULN; and
   bilirubin > 2 X ULN; and
   absence of alkaline phosphatase (AP) elevation.
2. Very high ALT cases:
   An increase of more than ten times the upper limit of the normal range in alanine aminotransferase (ALT>10ULN)

- Exclusion of patients with a diagnostic code also indicating other known causes of liver injury (cancer, alcoholism, alcohol related problems, gallbladder disease, pancreatic disease, and other chronic liver diseases not included in outcome definition) (codes listed in appendix 9.2.1).

For all identified events derived from Algorithm A and Algorithm B (in total 707 patients) the hospital medical records were manually reviewed to ascertain ALI status and cases were classified as either idiopathic or non-idiopathic ALI (see figure 1).

All 707 cases will be included, but idiopathic events (validated, n=194) and non-idiopathic events (false positives, n=494) will be analysed separately.

Figure 1. Case validation of all events of Acute Liver Injury (ALI) identified from the UPOD database 2008-2010 (* Overlap between categories, numbers do not add up).



	Definite a) ALT>2ULN	Definite b) AST>1ULN AP>1ULN BIL>1ULN	High ALT ALT>3ULN	Very high ALT>10ULN	Hy's law ALT>3ULN BIL>2ULN AP≤1ULN
ALI (total)	90	41	72	36	12
Non-idiopathic	47	28	39	21	7
Idiopathic	43	13	33	15	5
PPV	**48%**	**32%**	**46%**	**42%**	**42%**

Algorithm A
ICD-9-CM + lab

	Very high ALT>10ULN	Hy's law ALT>3ULN BIL>2ULN AP≤1ULN
	571	138
	421	108
	150	30
	26%	**22%**

Algorithm B
lab only

5. Study design: case control study

A case control study will be performed. All ALI cases detected within UPOD by the algorithms described above between January 2008 and December 2010 have been identified.

Record linkage of the ALI cases to the JHN and the ZGA databases will be performed.

The date of diagnosis (acute liver injury) or the date of first abnormal laboratory result meeting algorithm B conditions in case no acute liver injury diagnostic code is recorded will be considered the index date of the case.

Controls will be sampled from the patients at risk at the time of occurrence of the case (density or risk set sampling). Thus, for a given case, potential controls are all non-cases (without a code listed in appendix 9.2.2) at the time of the occurrence of the event, including future cases. Controls can therefore be cases later on. Controls will be individually matched to cases by age (within one year), sex, calendar date (month & year) and practice. We will select up to five controls per case. If less than 5 controls per case are identified, the matching criteria will be relaxed. First additional controls will be

selected within the same calendar year (any month), in a second step the age limits may be relaxed to age within three years.

Index date for the controls will be the index date of the assigned case.

5.1 Exposure definition

Exposure to antibiotics will be assessed in the primary care databases and in-hospital use as recorded in UPOD.

We will define patients as *current users* if a prescription for an antibiotic drug lasts until or after the index date or ends within 14 days prior to the index date; as *recent users* when supply of the most recent antibiotic drug prescription ended 15–90 days before the index date; *past use* when the supply of the most recent antibiotic drug prescription ended 91–365 days before the index date; and *non-use* when supply of the most recent antibiotic drug prescription ended more than 365 days before the index date or there was no recorded prescription at any time prior to the index date. We will use a window of 30 days prior to the index date as a secondary definition of current use. Current, recent and past exposure to antibiotics will be compared to the reference category of non use.

Furthermore, current use of antibiotics will be subdivided into two mutually exclusive categories: *single* when there is prescribing of only one individual type of antibiotic that lasts until the index date or ends within the 14 days before the index date, and *multiple* when the patient was prescribed more than one individual antibiotic type before the index date. Thus categories will include: non users of antibiotics, current single users; current multiple users, recent users and past users.

We will study the association of dose and duration of treatment among current users. Duration of use will be defined by the treatment period covering consecutive prescriptions. Prescriptions will be considered consecutive when less than 14 days elapse between them. We will categorize short duration as up to 7 days, medium 8- 21 days , and long > 21 days. Dose will be estimated among current users of individual drugs with sufficient use (e.g. amoxicillin): the most recent dosage instructions will be used to compute daily dose. We will classify low-medium dose when the prescribed dose is lower or equal the recommended dose for each individual presentation, and high if it is above that value.

Among current users, we will estimate the risk associated with different antibiotics drug class categorized in seven groups as defined in the protocol: tetracycline, penicillins & betalactamic, cephalosporin, macrolides, aminoglycosides, quinolones and other antibiotics and combinations (see appendix 9.3 for list of codes and groups).

5.2 Statistical Analyses

We will compute odds ratios (OR) and 95% confidence intervals of first occurrence of idiopathic acute liver injury (see outcome definition) associated with current use of antibiotics (as a group and different classes and individual drugs when possible) as compared to non-use with conditional logistic regression. Covariate variables will be introduced in the model to control for potential confounding. Also, dose and duration-relationships will be examined. We will construct different regression models, first including just the exposure and covariates in separate univariate models. A second model including general confounders (BMI, alcohol, smoking, and visits to GP). And finally we will also fit a full model including all potential confounders (comorbidities and drugs).

As the overlap between the two datasets is unknown, and hence the number of (exposed) cases available for analyses may be low, we will perform an additional multivariate model building strategy according to the following principles:

- according to the rule of thumb (1 confounder per 10 cases) determine the maximum number of confounders (n) to be selected in the multivariate model, based on the number of validated idiopathic cases that can be linked to GP records (e.g. if 40 of the 194 cases can be record linked, 4 confounders can be selected)

- select the best fitted model with exposure of interest and n covariates from the list of all potential confounders.

Separate analyses will be done for all cases identified according to the algorithm as well as for validated idiophatic ALI cases.

5.3 Handling of missing values

Missing information in the co-variables will be introduced in the model as a specific category ‘unknown’.

5.4 Blinding of results

During the statistical analysis and reporting phase, we will be blinded to the interim results from other studies on the same drug-adverse event pair.

5.5 Sample size

The table shows the number of cases needed given an alpha of 5% and a power of 80% for various percentages of exposure among controls and the odds ratios that can be detected. Method described by Dupont (9). With the estimated number of 194 validated idiopathic ALI cases described in 4.3 an odds ratio (OR) of 2.0 can be detected.

	Minimum odds ratio to detect		
Percentage exposed among controls	1.7	2.5	5.0
5%	526	283	34
10%	288	157	21
15%	211	117	17
20%	175	88	15

6. Covariates and potential confounders

Potential confounders will be measured at index date (date of onset of liver injury for both cases and their matched controls).

Different levels of potential confounders will be categorized:

a) General confounders:

- Age (continuous variable; and in ten-year categories : 0-9, 10-19, 20-29, 30-39, 40-49, 50-59, 60-69.70-79, 80-89, 90+)
- sex (male/female)
- Body mass index (kg/m2); and grouped in the following categories : < 18.5; 18.5-24.9 (ref) ; 25.0-29.9; ≥ 30 and unknown (most recent information max 5 years before the index date)
- Current smoking: non-smoker/current/past smoker/unknown (most recent information max 5 years before the index date)
- Alcohol use: no/yes/unknown (most recent information max 5 years before the index date)

- Health care use (number of visits to GP in previous year)

b) Specific risk factors possible associated with the outcome:

Disease history of (yes/no, ever recorded before) (codes listed in appendix 9.4)

- Heart failure
- Rheumatoid arthritis
- Diabetes

Comedication: *current users* if a prescription for an antibiotic drug lasts until or after the index date or ends within 30 days prior to the index date of (codes listed in appendix 9.5)

- Non-steroidal anti-inflammatory drug (NSAIDs)
- Other analgesics and antipyretics (paracetamol)
- Statins
- Antidepressants (including bupropion)
- Oral contraceptives
- Oral preparation for acne
- Disease-modifying anti-rheumatic drugs (DMARDs),
- Oral corticosteroids
- Antidiabetic drugs,
- Other hepatotoxic drugs (listed by FDA)

Co-morbidities will be identified by the recording of a ICPC code in the patient's clinical or referral files. Data on treatment with any concomitant medication will be identified in GP prescription files or in in-hospital medication files.

7.Timelines and Table shells

7.1 Timelines

The calendar below outlines the proposed timelines for the case control study.

Year	2013										
Month	1	2	3	4	5	6	7	8	9	10	11
	Mondriaan approval						Data analyses			Results report	Manus cript

7.2 Table shells for Case-Control analysis

Flow chart of record linkage:

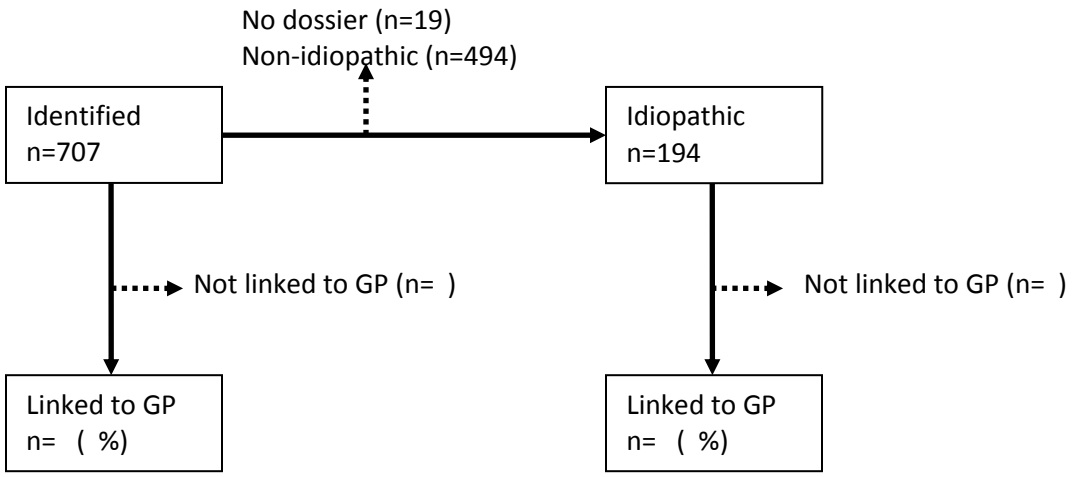


Table 1. Characteristics of GP-linked and non-linked cases.

	All cases (n=707)			Idiopathic cases (n=194)		
	Linked to GP (n=)	Not linked (n=)	p-value	Linked to GP (n=)	Not linked (n=)	p-value
Age (mean, sd)						
Sex (female, %)						
Drug-associated (n,%)						

Tables 2 to 5 below will be constructed for:

- all identified cases (those that can be record linked out of the initial n=707) and matched controls, 14 days time window for current antibiotic use
- validated idiopathic cases (those that can be record linked out of the initial n=194) and matched controls, 14 days time window for current antibiotic use
- non-idiopathic events (those that can be record linked out of the initial n=494) and matched controls, 14 days time window for current antibiotic use
- all identified cases (those that can be record linked out of the initial n=707) and matched controls, 30 days time window for current antibiotic use
- validated cases (those that can be record linked out of the initial n=194) and matched controls, 30 days time window for current antibiotic use
- non-idiopathic events (those that can be record linked out of the initial n=494) and matched controls, 30 days time window for current antibiotic use

Table 2. General confounders and life style factors assessed as risk factors for Idiopathic Acute liver injury (ALI)

	Controls		Cases		Crude OR (95% CI)	Adjusted OR* (95 %CI)
	No.	%	No.	%		
Male					NA	NA
Age					NA	NA
0-9					NA	NA
10-19					NA	NA
20-29					NA	NA
30-39					NA	NA
40-49					NA	NA
50-59					NA	NA
60-69					NA	NA
70-79					NA	NA
80-89					NA	NA
90+					NA	NA
Body mass index (kg/m^2)						
<18.5						
18.5-24.9					ref	
25-29						
>= 30						
unknown						
Smoking						
Non smoker					ref	
Smoker						
Exsmoker						
Unkown						
Alcohol consumption						

no					ref	
yes						
unknown						
Visits to GP previous year						
None					ref	
1-3						
4-10						
11+						

* OR adjusted by general confounders (all variables in the table)

Table 3. Use of antibiotics and Specific Co-morbidity and Co-medication assessed as risk factors for Idiopathic Acute liver injury (ALI)

	Controls		Cases		Crude OR (95% CI)	Adjusted OR* (95 %CI)	MultiAdjusted OR ** (95% CI)
	No.	%	No.	%			
Use of antibiotics							
No use >365							
Current (0-14 d)							
Recent (15-90)							
Past (91-365)							
Co-morbidities ever before							
Heart failure							
Rheumatoid arthritis							
Diabetes Mellitus							
Co-medications (current use)							
Non-steroidal anti-inflammatory drug (NSAIDs)							
Other analgesics /antipyretics							
Statins							
Oral contraceptives (females)							
Oral preparation for acne							
Disease-modifying anti-rheumatic drug (DMARD),							
Oral corticosteroids							
Antidiabetic drugs							
Antidepressants							
Other hepatotoxic drugs (FDA list)							

* Adjusted OR (by general confounders= variables in previous table) ** Multiadjusted OR (adjusted by general and specific confounders = variables in this table and previous table)

Table 4. Risk of Idiopathic Acute liver injury (ALI) associated with duration of use of antibiotics

	Controls		Cases		Crude OR (95% CI)	Adjusted OR* (95 %CI)	MultiAdjusted OR (95% CI)
	No.	%	No.	%			

Use of antibiotics num Rx							
No use							
Current short (7 days)							
Current medium (8-21 days)							
Current long (>21 days)							
Recent/past							

We will also analysed other time windows for duration (14 days)

Table 5. Risk of Idiopathic Acute liver injury (ALI) associated to type of antibiotics

	Controls		Cases		Crude OR (95% CI)	Adjusted OR* (95 %CI)	MultiAdjusted OR (95% CI)
	No.	%	No.	%			
Use of antibiotics							
No use							
Current							
1. Tetracyclines							
2. Penicillins& betalactamics							
3. Cephalosporin							
4. Macrolides							
5. Aminoglycosid							
6. Quinolones							
7. Other antibiotics & combinations							
Recent/ past							

* Type of antibiotics will also be collapse into 5 groups (betalactamics&penicilins; Other betalactamics; Cephalosporins; Macrolides; Quinolones; Other antibiotics&combinations) if number of cases are small

8. References

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9. Dupont WD. Power calculations for matched case-control studies. Biometrics. 1988;44(4):1157-68.

9. Appendices

9.1 Code list for Outcome(s) of interest

9.1.1 ICD-9 codes for Idiopathic Acute Liver injury

DISEASES	
570	Acute and subacute necrosis of liver Acute hepatic failure Acute or subacute hepatitis, not specified as infective Necrosis of liver (acute) (diffuse) (massive) (subacute) Parenchymatous degeneration of liver Yellow atrophy (liver) (acute) (subacute) Excludes: icterus gravis of newborn (773.0-773.2) serum hepatitis (070.2-070.3) that with: abortion (634-638 with .7, 639.8) ectopic or molar pregnancy (639.8) pregnancy, childbirth, or the puerperium (646.7) viral hepatitis (070.0-070.9)
572.2	Hepatic coma Hepatic encephalopathy Hepatocerebral intoxication Portal-systemic encephalopathy Excludes: Hepatic coma associated with viral hepatitis
572.4	Hepatorenal syndrome Excludes: that following delivery (674.8)
573.3	Hepatitis, unspecified Toxic (non-infectious) hepatitis Use additional E code to identifiy cause
573.9	Unspecified disorder of liver
SYMPTOMS	
782.4	Jaundice, unspecified, not of newborn Cholemia NOS Icterus NOS Excludes: Jaundice in newborn (774.0-774.7) Due to immunization (773.0-773.2, 773.4)
789.1	Hepatomegaly

	Enlargement of liver
789.59	Other ascites
790.4	Nonspecific elevation of levels of transaminase or lactic acid dehydrogenase [LDH]
790.5	Other nonspecific abnormal serum enzyme levels Abnormal serum level of: Acid phosphatise Alkaline phosphatise Amylase Lipase Excludes: Deficiency of circulating enzymes (277.6)
791.4	Biliuria
794.8	Abnormal results of liver function Abnormal liver scan
PROCEDURES	
50.1	50.11 Closed (percutaneous) [needle] biopsy of liver Diagnostic aspiration of liver 50.12 Open biopsy of liver Wedge biopsy 50.13 Transjugular liver biopsy Transvenous liver biopsy Excludes: closed (percutaneous) [needle] biopsy of liver (50.11) laparoscopic liver biopsy (50.14) 50.14 Laparoscopic liver biopsy Excludes: closed (percutaneous) [needle] biopsy of liver (50.11) open biopsy of liver (50.12) transjugular liver biopsy (50.13) 50.19 Other diagnostic procedures on liver Excludes: laparoscopic liver biopsy (50.14) liver scan and radioisotope function study (92.02) microscopic examination of specimen from liver (91.01-91.09) transjugular liver biopsy (50.13) Diagnostic procedures on liver
50.5	Liver transplant

	50.5 Liver transplant 50.51 Auxiliary liver transplant Auxiliary hepatic transplantation leaving patient's own liver in situ 50.59 Other transplant of liver
50.91	Percutaneous aspiration of liver Excludes: Percutaneous biopsy (50.11)

9.2 Code list for Exclusion criteria for outcome

9.2.1 ICD-9 codes for exclusion criteria

Cancer	
155	Malignant neoplasm of liver and intrahepatic bile ducts 155.0 Liver, primary 155.1 Intrahepatic bile ducts 155.2 Liver, not specified as primary or secondary
197.7	Secondary malignant neoplasm of liver, specified as secondary
Gallbladder diseases/ Cholelithiasis/ cholecystitis/ Cholangitis	
574	Cholelithiasis
575	Other diseases of gallbladder
576	Other diseases of biliary tract
Diseases of pancreas / pancreatitis/ other diseases of pancreas	
577	Diseases of pancreas
Other chronic liver disease (including autoimmune hepatitis)	
571.4	Chronic hepatitis Excludes: Viral hepatitis (acute) (chronic) (070.0-070.9) 571.40 chronic hepatitis, unspecified 571.41 chronic persistent hepatitis 571.42 autoimmune hepatitis 571.49 other Chronic hepatitis: active aggressive Recurrent hepatitis
070 (070.0-0.70.9)	Viral hepatitis (acute) (chronic)
571.8	Other chronic non-alcoholic liver disease

	Chronic yellow atrophy (liver) Fatty liver, without mention of alcohol
571.9	Unspecified chronic liver disease without mention of alcohol

9.2.2 ICPC codes for exclusion criteria

ICPC codes Description

A79 Malignancy NOS
B72 Hodgkin's disease/lymphoma
B73 Leukaemia
B74 Malignant neoplasm blood other
D74 Malignant neoplasm stomach
D75 Malignant neoplasm colon/rectum
D76 Malignant neoplasm pancreas
D77 Malignant neoplasm digest other/NOS
F74 Neoplasm of the eye/adnexa
H75 Neoplasm of ear
K72 Neoplasm cardiovascular
L71 Malignant neoplasm musculoskeletal
N74 Malignant neoplasm nervous system
R84 Malignant neoplasm bronchus/lung
R85 Malignant neoplasm respiratory, other
S77 Malignant neoplasm of the skin
T71 Malignant neoplasm thyroid
U75 Malignant neoplasm of kidney
U76 Malignant neoplasm of bladder
U77 Malignant neoplasm urinary other
W72 Malignant neoplasm relate to pregnancy
X75 Malignant neoplasm cervix
X76 Malignant neoplasm breast female
X77 Malignant neoplasm genital other (f)
Y77 Malignant neoplasm prostate
Y78 Malignant neoplasm genital other (m)

D13 Jaundice
D72 Viral hepatitis
D96 Hepatomegaly
D97 Liver disease nos
D98 Cholecystitis/cholelithiasis
D99.04 Pancreatitis
P15 Chronic alcohol abuse
P16 Acute alcohol abuse

9.3 Code list for Drug: Exposure(s) of interest

ATC codes	ATC Description
J01A	TETRACYCLINES
J01AA	tetracyclines
J01AA01	demeclocycline
J01AA02	doxycycline
J01AA03	chlortetracycline
J01AA04	lymecycline
J01AA05	metacycline
J01AA06	oxytetracycline
J01AA07	tetracycline
J01AA08	minocycline
J01AA09	rolitetracycline
J01AA10	penimepicycline
J01AA11	clomocycline
J01AA12	tigecycline
J01AA20	combinations of tetracyclines
J01AA56	oxytetracycline, combinations

PROTOCOL GROUP 2: beta-lactam antibacterias, penicillins

ATC code	Name
J01C	BETA-LACTAM ANTIBACTERIALS, PENICILLINS
J01CA	penicillins with extended spectrum
J01CA01	ampicillin
J01CA02	pivampicillin
J01CA03	carbenicillin
J01CA04	amoxicillin
J01CA05	carindacillin
J01CA06	bacampicillin
J01CA07	epicillin
J01CA08	pivmecillinam
J01CA09	azlocillin
J01CA10	mezlocillin
J01CA11	mecillinam
J01CA12	piperacillin
J01CA13	ticarcillin
J01CA14	metampicillin
J01CA15	talampicillin
J01CA16	sulbenicillin
J01CA17	temocillin

J01CA18	hetacillin
J01CA19	aspoxicillin
J01CA20	combinations
J01CA51	ampicillin, combinations
J01CE	beta-lactamase sensitive penicillins
J01CE01	benzylpenicillin
J01CE02	phenoxymethylpenicillin
J01CE03	propicillin
J01CE04	azidocillin
J01CE05	pheneticillin
J01CE06	penamecillin
J01CE07	clometocillin
J01CE08	benzathine benzylpenicillin
J01CE09	procaine benzylpenicillin
J01CE10	benzathine phenoxymethylpenicillin
J01CE30	combinations
J01CF	beta-lactamase resistant penicillins
J01CF01	dicloxacillin
J01CF02	cloxacillin
J01CF03	meticillin
J01CF04	oxacillin
J01CF05	flucloxacillin
J01CG	beta-lactamase inhibitors
J01CG01	sulbactam
J01CG02	tazobactam
J01CR	combinations of penicillins, incl. beta-lactamase inhibitors
J01CR01	ampicillin and enzyme inhibitor
J01CR02	amoxicillin and enzyme inhibitor
J01CR03	ticarcillin and enzyme inhibitor
J01CR04	sultamicillin
J01CR05	piperacillin and enzyme inhibitor
J01CR50	combinations of penicillins

PROTOCOL GROUP 3: other beta-lactams: cephalosporins

ATC code	Name
J01D	OTHER BETA-LACTAM ANTIBACTERIALS
J01DB	first-generation cephalosporins
J01DB01	cefalexin
J01DB02	cefaloridine
J01DB03	cefalotin
J01DB04	cefazolin

J01DB05	cefadroxil
J01DB06	cefazedone
J01DB07	cefatrizine
J01DB08	cefapirin
J01DB09	cefradine
J01DB10	cefacetrile
J01DB11	cefroxadine
J01DB12	ceftezole
J01DC	second-generation cephalosporins
J01DC01	cefoxitin
J01DC02	cefuroxime
J01DC03	cefamandole
J01DC04	cefaclor
J01DC05	cefotetan
J01DC06	cefonicid
J01DC07	cefotiam
J01DC08	loracarbef
J01DC09	cefmetazole
J01DC10	cefprozil
J01DC11	ceforanide
J01DC12	cefminox
J01DC13	cefbuperazone
J01DC14	flomoxef
J01DD	third-generation cephalosporins
J01DD01	cefotaxime
J01DD02	ceftazidime
J01DD03	cefsulodin
J01DD04	ceftriaxone
J01DD05	cefmenoxime
J01DD06	latamoxef
J01DD07	ceftizoxime
J01DD08	cefixime
J01DD09	cefodizime
J01DD10	cefetamet
J01DD11	cefpiramide
J01DD12	cefoperazone
J01DD13	cefpodoxime
J01DD14	ceftibuten
J01DD15	cefdinir
J01DD16	cefditoren
J01DD17	cefcapene

J01DD54	ceftriaxone, combinations
J01DD62	cefoperazone, combinations
J01D	OTHER BETA-LACTAM ANTIBACTERIALS
J01DE	fourth-generation cephalosporins
J01DE01	cefepime
J01DE02	cefpirome
J01DE03	cefozopran
J01DF	monobactams
J01DF01	aztreonam
J01DF02	carumonam
J01DH	carbapenems
J01DH02	meropenem
J01DH03	ertapenem
J01DH04	doripenem
J01DH05	biapenem
J01DH51	imipenem and enzyme inhibitor
J01DH55	panipenem and betamipron
J01DI	other cephalosporins
J01DI01	ceftobiprole medocaril
J01DI02	ceftaroline fosamil

PROTOCOL GROUP 4: macrolides, lincosamides and streptogramins

ATC code	Name
J01F	MACROLIDES, LINCOSAMIDES AND STREPTOGRAMINS
J01FA	macrolides
J01FA01	erythromycin
J01FA02	spiramycin
J01FA03	midecamycin
J01FA05	oleandomycin
J01FA06	roxithromycin
J01FA07	josamycin
J01FA08	troleandomycin
J01FA09	clarithromycin
J01FA10	azithromycin
J01FA11	miocamycin
J01FA12	rokitamycin
J01FA13	dirithromycin
J01FA14	flurithromycin
J01FA15	telithromycin
J01FF	lincosamides
J01FF01	clindamycin

J01FF02	lincomycin
J01FG	streptogramins
J01FG01	pristinamycin
J01FG02	quinupristin/dalfopristin

PROTOCOL GROUP 5: aminoglycosides

ATC code	Name
J01G	AMINOGLYCOSIDE ANTIBACTERIALS
J01GA	streptomycins
J01GA01	streptomycin
J01GA02	streptoduocin
J01GB	other aminoglycosides
J01GB01	tobramycin
J01GB03	gentamicin
J01GB04	kanamycin
J01GB05	neomycin
J01GB06	amikacin
J01GB07	netilmicin
J01GB08	sisomicin
J01GB09	dibekacin
J01GB10	ribostamycin
J01GB11	isepamicin
J01GB12	arbekacin
J01GB13	bekanamycin

PROTOCOL GROUP 6: quinolones

ATC code	Name
J01M	QUINOLONE ANTIBACTERIALS
J01MA	fluoroquinolones
J01MA01	ofloxacin
J01MA02	ciprofloxacin
J01MA03	pefloxacin
J01MA04	enoxacin
J01MA05	temafloxacin
J01MA06	norfloxacin
J01MA07	lomefloxacin
J01MA08	fleroxacin
J01MA09	sparfloxacin
J01MA10	rufloxacin
J01MA11	grepafloxacin
J01MA12	levofloxacin

J01MA13	trovafloxacin
J01MA14	moxifloxacin
J01MA15	gemifloxacin
J01MA16	gatifloxacin
J01MA17	prulifloxacin
J01MA18	pazufloxacin
J01MA19	garenoxacin
J01MA21	sitafloxacin
J01MB	other quinolones
J01MB01	rosoxacin
J01MB02	nalidixic acid
J01MB03	piromidic acid
J01MB04	pipemidic acid
J01MB05	oxolinic acid
J01MB06	cinoxacin
J01MB07	flumequine

PROTOCOL GROUP 7: Other antibiotics (anphenicols, suphonamides & others combinations)

ATC code	Name
J01E	SULFONAMIDES AND TRIMETHOPRIM
J01EA	trimethoprim and derivatives
J01EA01	trimethoprim
J01EA02	brodimoprim
J01EA03	iclaprim
J01EB	short-acting sulfonamides
J01EB01	sulfaisodimidine
J01EB02	sulfamethizole
J01EB03	sulfadimidine
J01EB04	sulfapyridine
J01EB05	sulfafurazole
J01EB06	sulfanilamide
J01EB07	sulfathiazole
J01EB08	sulfathiourea
J01EB20	combinations
J01EC	intermediate-acting sulfonamides
J01EC01	sulfamethoxazole
J01EC02	sulfadiazine
J01EC03	sulfamoxole
J01EC20	combinations
J01ED	long-acting sulfonamides
J01ED01	sulfadimethoxine

J01ED02	sulfalene
J01ED03	sulfametomidine
J01ED04	sulfametoxydiazine
J01ED05	sulfamethoxypyridazine
J01ED06	sulfaperin
J01ED07	sulfamerazine
J01ED08	sulfaphenazole
J01ED09	sulfamazone
J01ED20	combinations
J01EE	combinations of sulfonamides and trimethoprim, incl. derivatives
J01EE01	sulfamethoxazole and trimethoprim
J01EE02	sulfadiazine and trimethoprim
J01EE03	sulfametrole and trimethoprim
J01EE04	sulfamoxole and trimethoprim
J01EE05	sulfadimidine and trimethoprim
J01EE06	sulfadiazine and tetroxoprim
J01EE07	sulfamerazine and trimethoprim
J01B	AMPHENICOLS
J01BA	amphenicols
J01BA01	chloramphenicol
J01BA02	thiamphenicol
J01BA52	thiamphenicol, combinations
J01R	COMBINATIONS OF ANTIBACTERIALS
J01RA	combinations of antibacterials
J01RA01	penicillins, combinations with other antibacterials
J01RA02	sulfonamides, combinations with other antibacterials (excl. trimethoprim)
J01RA03	cefuroxime, combinations with other antibacterials
J01RA04	spiramycin, combinations with other antibacterials
J01X	OTHER ANTIBACTERIALS
J01XA	glycopeptide antibacterials
J01XA01	vancomycin
J01XA02	teicoplanin
J01XA03	telavancin
J01XA04	dalbavancin
J01XA05	oritavancin
J01XB	polymyxins
J01XB01	colistin
J01XB02	polymyxin B
J01XC	steroid antibacterials
J01XC01	fusidic acid
J01XD	imidazole derivatives

J01XD01	metronidazole
J01XD02	tinidazole
J01XD03	ornidazole
J01XE	nitrofuran derivatives
J01XE01	nitrofurantoin
J01XE02	nifurtoinol
J01XX	other antibacterials
J01XX01	fosfomycin
J01XX02	xibornol
J01XX03	clofoctol
J01XX04	spectinomycin
J01XX05	methenamine
J01XX06	mandelic acid
J01XX07	nitroxoline
J01XX08	linezolid
J01XX09	daptomycin
J01XX10	bacitracin

9.4 Code list for Potential confounding factors - diseases/diagnoses

K77 Heart failure
L88 Rheumatoid/seropositive arthritis
T89 Diabetes insulin dependent
T90 Diabetes non-insulin dependent

9.5 Code list for Potential confounding factors - drugs

Non-steroidal anti-inflammatory drug (NSAIDs)

ATC codes	Name
M01A	ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS
M01AA	Butylpyrazolidines
M01AB	Acetic acid derivatives and related substances
M01AC	Oxicams
M01AE	Propionic acid derivatives
M01AG	Fenamates
M01AH	Coxibs
M01AX	Other antiinflammatory and antirheumatic agents, non-steroids

Other analgesics and antipyretics (Paracetamol)

ATC codes	ATC description
N02BA	Salicylic acid and derivatives
N02BB	Pyrazolones
N02BE	Anilides (Paracetamol and combination)
N02BG	Other analgesics and antipyretics

Statins

ATC codes	Name
C10AA	HMG CoA reductase inhibitors
C10AA01	simvastatin
C10AA02	lovastatin
C10AA03	pravastatin
C10AA04	fluvastatin
C10AA05	atorvastatin
C10AA06	cerivastatin
C10AA07	rosuvastatin
C10AA08	pitavastatin
C10BX	HMG CoA reductase inhibitors, other combinations
C10BX01	simvastatin and acetylsalicylic acid
C10BX02	pravastatin and acetylsalicylic acid
C10BX03	atorvastatin and amlodipine
C10BX04	simvastatin, acetylsalicylic acid and ramipril
C10BA	HMG CoA reductase inhibitors in combination with other lipid modifying agents
C10BA01	lovastatin and nicotinic acid
C10BA02	simvastatin and ezetimibe
C10BA03	pravastatin and fenofibrate

Antidepressants

ATC codes	ATC description
N06AA	Non-selective monoamine reuptake inhibitors
N06AB	Selective serotonin reuptake inhibitors
N06AF	Monoamine oxidase inhibitors, non-selective
N06AG	Monoamine oxidase A inhibitors
N06AX	Other antidepressants (N06AX 12 Bupropion)

Oral contraceptives

ATC codes	ATC description
G03A	HORMONAL CONTRACEPTIVES FOR SYSTEMIC USE
G03AA	Progestogens and estrogens, fixed combinations
G03AB	Progestogens and estrogens, sequential preparations
G03AD	Emergency contraceptives

Oral preparations for acne (combination)

ATC codes	ATC description
D10B A01	ISOTRETINOIN
G03H B01	CYPROTERONE AND ESTROGEN
G03H A01	CYPROTERONE

Drugs disease-modifying anti-rheumatic drugs (DMARDs)

ATC codes	Description
Gold	
M01CB03	Auranofin
M01CB02	Sodium aurothiomalate
Penicillamine	
M01CC01	Penicillamine
Antimalarials	
P01BA01	Chloroquine
P01BA02	Hydroxychloroquine sulphate
Drugs affecting the immune response	
L04AX01	Azathioprine
L04AD01	Cyclosporine
L04AA13	Leflunomide
L01BA01/L01AX03	Methotrexate
Cytokine modulators	
L04AA24	Abatacept
L04AB04	Adalimumab
L04AC03	Anakinra
L04AB01	Etanercept
L04AB02	Infliximab
L01XC02	Rituximab
Sulfasalazine	
A07EC01	Sulfasalazine

Oral Corticosteroids

ATC codes	Description
H02A	Corticosteroids for systemic use
H02AA	Mineralocorticoids
H02AB	Glucocorticoids
H02B	Corticosteroids for systemic use, combinations
H02BX	Corticosteroids for systemic use, combinations
A07E	Intestinal antiinflammatory agents
A07EA	Corticosteroids acting locally
MO1B	Anti-inflammatory/ antirheumatic agents in combination
MO1BA	Antiinflammatory/ antirheumatic agents in combination with corticosteroids

Antidiabetic drugs

ATC codes	Description
A10A	Insulins and analogues

A10AB	Insulins and analogues for injection, fast-acting
A10AC	Insulins and analogues for injection, intermediate-acting
A10AD	Insulins and analogues for injection, intermediate-acting combined with fast-acting
A10AE	Insulins and analogues for injection, long-acting
A10AF	Insulins and analogues for inhalation
A10B	Blood glucose lowering drugs, excluding insulins
A10BA	Biguanides
A10BB	Sulfonamides, urea derivatives
A10BC	Sulfonamides (heterocyclic)
A10BD	Combinations of oral blood glucose lowering drugs
A10BF	Alpha glucosidase inhibitors
A10BG	Thiazolidinediones
A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors
A10BX	Other blood glucose lowering drugs, excluding insulins
A10X	Other drugs used in diabetes
A10XA	Aldose reductase inhibitors

Other hepatotoxic drugs not included in above groups (listed by the FDA)

ATC codes	Description
A07EC02	mesalazine
A07EC03	olsalazine
C02DB01	dihydralazine
C02DB02	hydralazine
C02LG01	dihydralazine and diuretics
C02LG02	hydralazine and diuretics
C02LG51	dihydralazine and diuretics, combinations
C03CC02	ticrynafen (tienilic acid)
C04AC	nicotinic acid and derivates
C07AG01	labetalol
C07BG01	labetalol and thiazides
C07CG01	labetalol and diuretics
C10AD	nicotinic acid and derivates
C10BA01	lobastatin and nicotinic acid
J01XE01	nitrofurantoin
J04AC	hydrazides (isoniazid)
J04AM	combination drugs for treatment of TBC (isoniazid)
M03CA	dantrolene and derivates
M03CA01	dantrolene
M04AA01	allopurinol
M04AA51	allopurinol combinations
N03AA01	methylphenobarbital
N03AA02	phenobarbital
N03AB	antiepileptic Hydantoin derivatives (phenytoin)
N03AF01	carbamazepine
N03AG01	valproic acid
N03AG02	valpromide
N03AX10	felbamate
N04BX01	tolcapone
N05AA01	chlorpromazine

N05AB04	prochlorperazine
N05AC02	thioridazine
N05AD01	haloperidol
N06AA02	imipramine
N06AA03	imipramine oxide
N06AA06	trimipramine
N06AF05	iproniazid
N06BA05	pemoline

9.6 Reference values for liver related laboratory results

Liver tests	Reference value
Alanine transaminase (ALT)	Male <45 U/L
	Female <35 U/L
Aspartate transaminase (AST)	Male <35 U/L
	Female <30 U/L
Alkaline phosphatase (AP)	<120 U/L
Bilirubin	<21 µmol/L