CLINICAL TRIAL RESULTS INFORMATION	
ADMINISTRATIVE INFORMATION	Protocol number : CHUBX 2014/39 EUDRACT number: NA IDRCB number : NA Trial report number : Date of trial report : 31/10/2019 Is the trial part of a Paediatric Investigation Plan? No
TRIAL DESIGN	***Principle trial design*** *(e.g., randomized, open, single-blinded etc)* Empirical assessment of case-control designs (self-controlled case series, case-population, case control) on data from the French national healthcare claims database (SNDS) for the identification of acute liver injuries (ALI), acute kidney injuries (AKI), myocardial infarctions (MI) and upper gastrointestinal bleedings (UGIB).
BACKGROUND FOR CONDUCTING THE TRIAL	***Scientific background and explanation of rationale for the trial*** The increasing accessibility of population databases has brought new opportunities to identify drug-related alerts, using very different methods from those used to analyze spontaneous reporting data. A number of initiatives have been undertaken at the international level to develop methods and systems for safety signal identification and evaluation in longitudinal healthcare databases. Amongst them, the Observational Medical Outcomes Partnership (OMOP) performed an empirical assessment of analytical methods for signal identification in standardized healthcare data and evaluated the performance of various methods in five US and six European observational databases through a reference set composed of positive and negative drug controls across four health outcomes of interest: ALI, AKI, MI and UGIB. France has a large nationwide longitudinal claims and hospital database, the SNDS, which currently includes about 99,9% of the French population (66.6 million persons), from birth or immigration to death or emigration, including all reimbursed medical and paramedical encounters. Since SNDS systematically and prospectively captures drug dispensings and events leading to hospital stays, including death, it has a strong potential for detection of drug safety signals, even early ones. SNDS was not available at the time, thus it was not included in the OMOP experiment. The case-population design (CP), a case-based approach where drug exposure in cases is compared to aggregate data from the entire population was not included either. This design seems yet well suited to the alert generation environment, providing absolute event rates in addition to the relative risks or odds ratios also found from other case-based approaches. ALCAPONE project (Alert generation using the case population approach), aimed to empirically compare and calibrate within SNDS case-based methods – self-controlled case series (SCCS), case-control (CC) and CP – using the OMOP methodology to determine which one better fit the database to generate safety alerts regarding drugs associated with ALI, AKI, UGIB and MI.

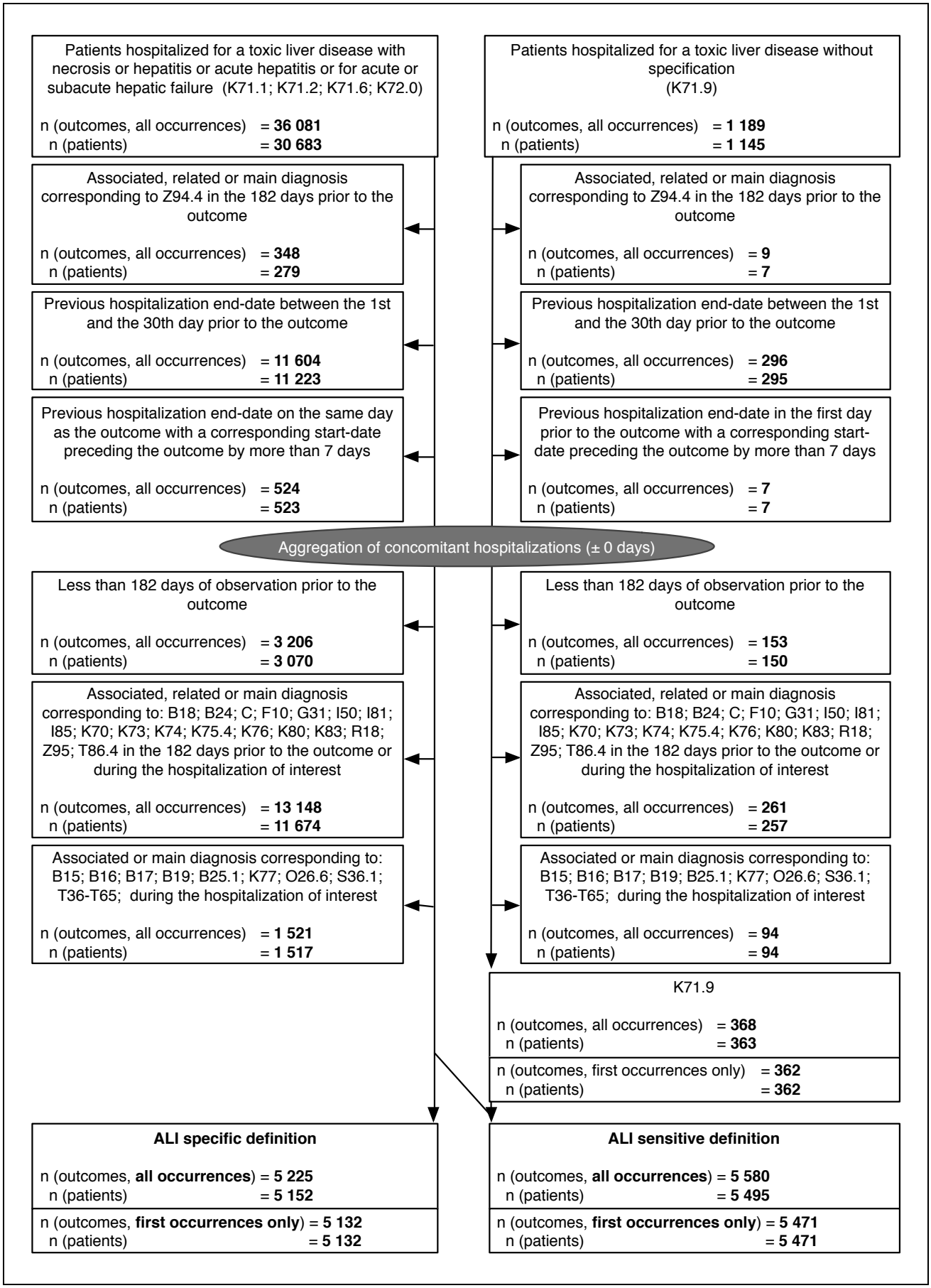
PARTICIPANTS OF THE TRIAL	***Eligibility criteria for participants*** *Inclusion criteria* - Patients presenting ALI, AKI, MI or UGIB between 01/01/2009 and 31/12/2014 - And having at least 182 days of healthcare history *Exclusion criteria* - AKI: patients presenting previous renal transplantation or metal intoxication or specific kidney diseases - ALI: patients presenting liver injury resulting from other causes than potential drug toxicity (*e.g.* chronic viral hepatitis, alcoholic liver disease, *etc*.) ALI, AKI, MI and UGIB were detected in the SNDS using primary diagnosis from hospital discharge summaries captured by the PMSI. For each outcome, a sensitive and a specific definitions were defined. ***Settings and locations where the data were collected*** Data were extracted from the *Système National des Données de Santé* (SNDS) covering 99% of the French population and gathering claims data from the *Système National d'Informations Inter-Régimes de l'Assurance Maladie* (SNIIRAM), hospital discharge summaries from the *Programme de médicalisation des systèmes d'information* (PMSI) and national death data from the National Death Registry. The 1/97th sample of the SNDS, the *Echantillon généraliste de bénéficiaires* (EGB) was also used.
INTERVENTIONS	***Precise details of the interventions intended for each group and how and when they were actually administered.*** *Includes statement of precise dose, treatment duration, control interventions, additional treatment for each arm of the trial.* Since this is an observational study, there is no intervention. For each health outcome of interest (ALI, AKI, MI and UGIB) a specific collection of positive and negative drug controls was defined and used to assess the performance of different methodological approaches. Positive controls are drugs with a known association with the outcome. Negative controls are drugs with no evidence to support causal association with the outcomes. These controls result from two reference sets used in previous experiments (OMOP and EU-ADR), and adapted to drug availability on the French market. Exposure was captured through SNDS dispensing data. Power computation was performed to ensure their correct detection. Number of screened controls: - ALI: 58 positives and 23 negatives - AKI: 22 positives and 36 negatives - MI: 28 positives and 42 negatives - UGIB: 22 positives and 42 negatives
OBJECTIVE(S) OF THE TRIAL	***Specific objectives of the trial*** ***OBJECTIF PRINCIPAL :*** To determine in which extent, the French databases – the SNDS and the EGB – were suitable to perform drug safety signal detection, what

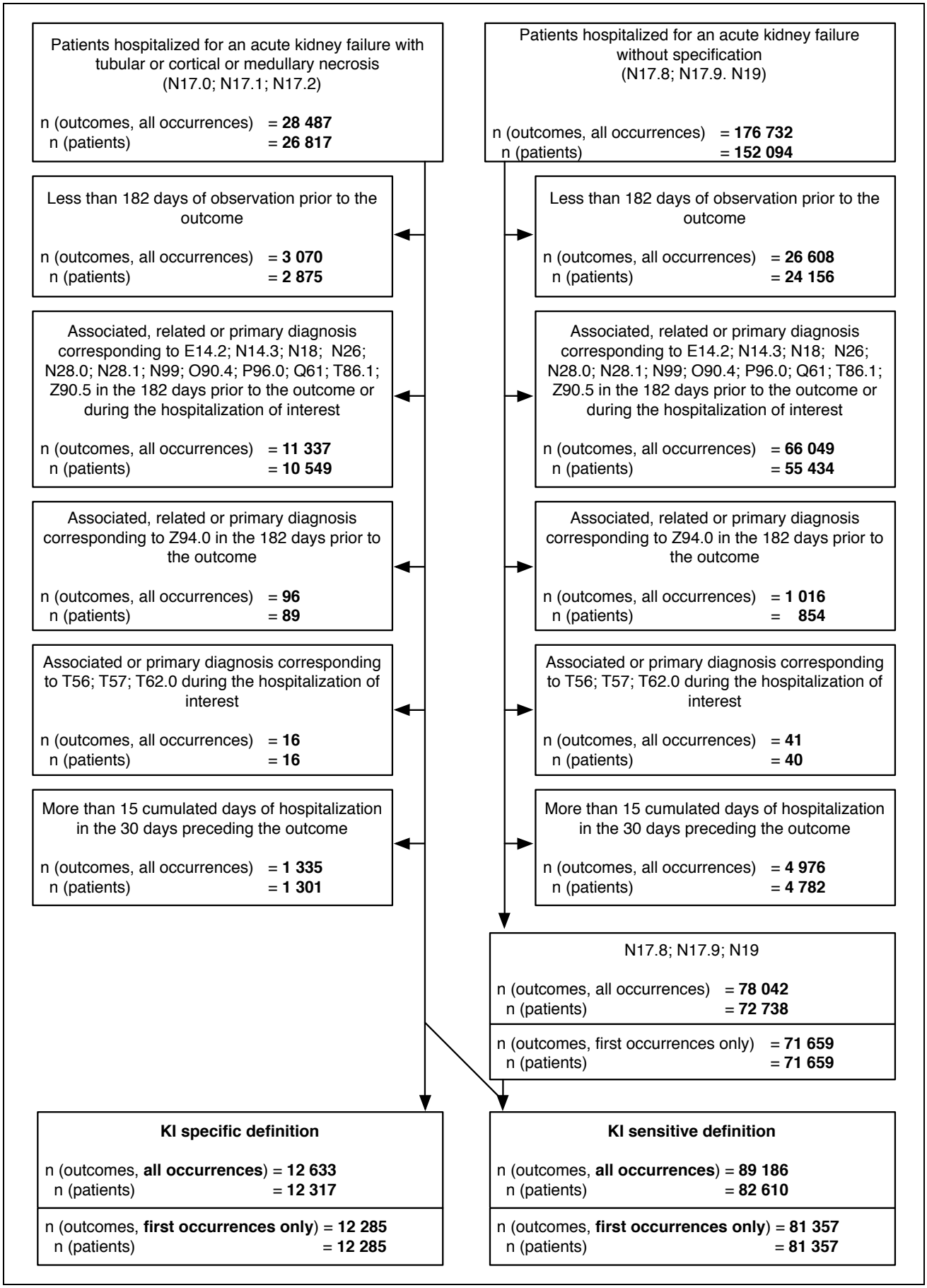
	methodology rather use to identify ALI, AKI, MI and UGIB related risk, and how accurate were the generated estimates. ***OBJECTIFS SPÉCIFIQUES :*** - To adapt the OMOP reference set to the SNDS - To develop the case-population approach in the SNDS - To assess the performances of SCCS, CC and CP in the SNDS for drug safety signal detection
OUTCOME MEASURES	***Clearly defined primary and important secondary outcome measures*** ***CRITÈRE DE JUGEMENT PRINCIPAL*** For each definition of each outcome the number of drug controls correctly detected by each design variant will be used to assess their performances through the calculation of - The sensitivity - The specificity - The area under the receiving operator curve (AUC) - The mean square error (for negative controls only) - The coverage probability (for negative controls only)
RANDOMISATION IMPLEMENTATION	This is an observational study in real life settings relying on SNDS data: randomization cannot be implemented. Confusion bias was addressed differently according to the different designs: - SCCS: using the case as its self-control, all time unvarying confounders were automatically adjusted. Model also adjusted for some time varying confounders such as age, seasonality or co-medication. - CC: cases were matched to controls on age and gender
BLINDING	***Information on blinding*** This study relied on secondary use of SNDS data. As initially data were prospectively and systematically collected for billing purposes, they are not affected by changes in patients or physicians behavior caused by research participation (Hawthorne effect).
ANALYSE STATISTIQUE DES DONNEES	***Statistical methods*** *used to compare groups for primary outcome(s). Any methods for additional analyses, such as subgroup analyses and adjusted analyses.* They are 4 main stages in the study process (I) the preparation of SNDS data to fit the OMOP common data model and the selection of the detectable positive and negative drug controls; (II) the application of 3 case-based designs: SCCS, CC and CP, including design variants for each method; (III) the assessment and comparison of design performance; and (IV) the identification of the best design variants and

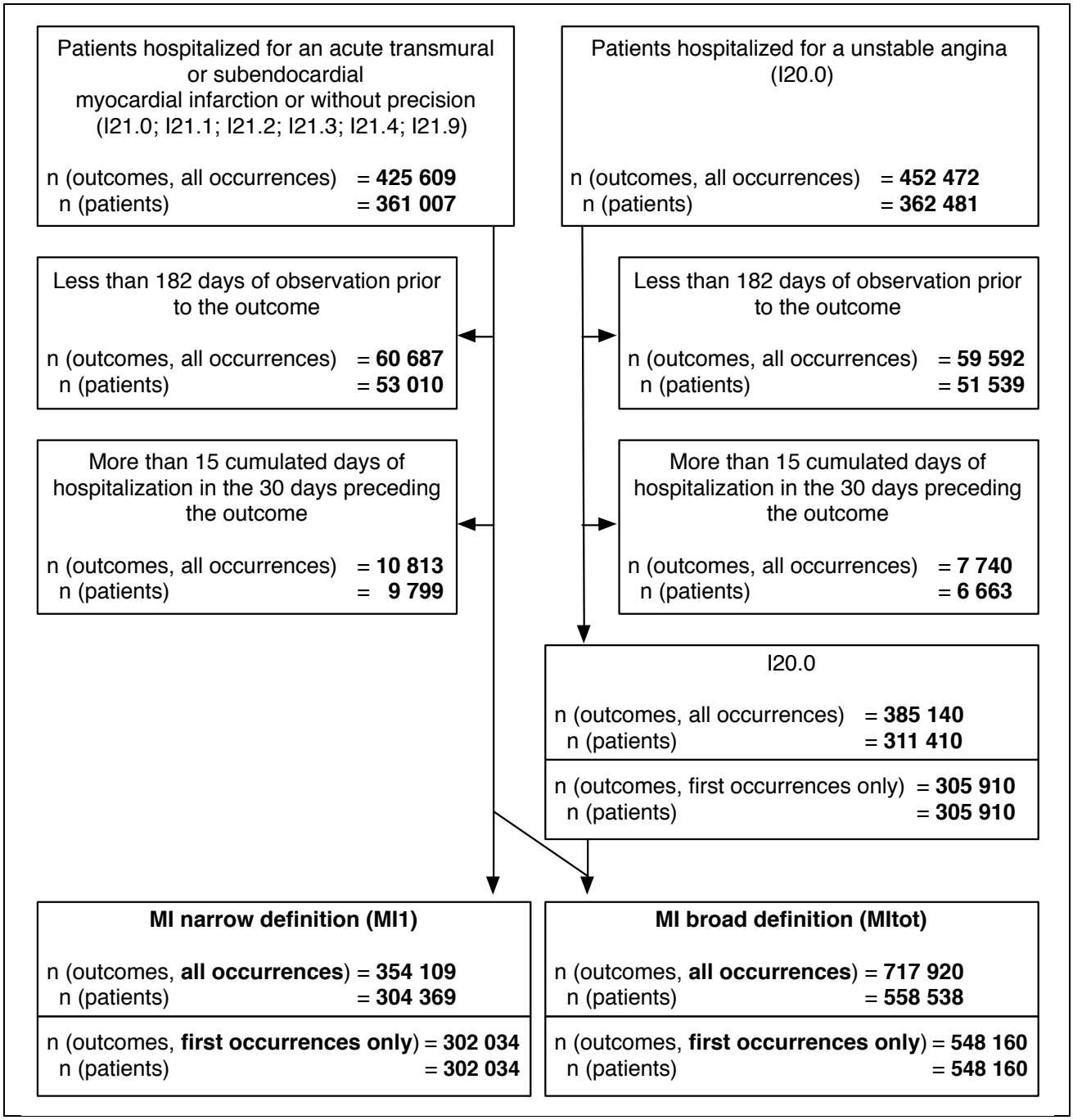
	their calibration. (II) To optimize machine time processing the MI, UGIB and AKI population were sampled at respectively 1/20th, 1/10th, and 1/3rd proportions before screening. The best variant of each approach was then replicated in the whole population. SCCS consists of comparing each case to itself: the event rate during periods exposed to the drug of interest is compared to the event rate during unexposed periods. A total of 96 SCCS variants were tested using OHDSI SelfControlledCaseSeries R package. The minimum duration of a subject for inclusion in the analysis was set to 182 days. Two different risk windows were considered: the full period covered by the drug dispensed or the 30 first days from dispensing. In order to address potential indication bias, three different pre-exposure windows were tested: 0, 7 or 30 days. The model was applied to all occurrences of the outcome or only to the first one. Some variants also adjusted for age, seasonality and for multiple drugs. CC methods compare the distribution of exposure prior to outcomes in cases with the distribution in patients at risk for the outcome. A total of 20 CC variants were tested using OHDSI CaseControl R package. Controls were selected from the EGB subjects that did not present with the HOI. The age of each potential control was calculated for each year of the data extraction sample (6 ages in total). Controls were matched with cases according to their gender and their age at index-date. Each selected control was given the same index date as their corresponding case. The number of controls per case was set to 2 or 10 according to the variant. Unmatched cases were removed. To be included, cases and controls must have had at least 182 days of observation prior to their "index date". When only the first occurrence of the HOI was considered, the patient was excluded if it occurred within the 182 days of the washout period. To address protopathic and confounding by indication a lag period of 7 or 15 days was introduced before the event onset in some variants. The risk windows applied was of 7, 30 or 60 days. CP methods compare exposure distribution among cases and controls consisting of the complete population. Exposure distribution for the complete population was extrapolated from the EGB over the study period using 1) an age and sex stratified extrapolation, and 2) a raw extrapolation (i.e. no stratification on age or sex). To be included in the case group or the aggregated control data, a patient had to be enrolled in the database for at least 182 days. Risk windows, exclusion periods and outcome selection were defined in same way as for CC. Two approaches were tested: (1) a count data approach, considering the number of patients exposed or not in the control population; and (2) a person-time approach, considering the person-time units of exposure in the reference population. (e.g. person-months). Two measures of associations were calculated: the case population ratio (CPR), and the predicted relative risk (pRR). In the CPR calculation we assumed that the number of cases and the exposure rate are so small that the overall number of cases and the overall population can respectively approximate the number of unexposed cases and the unexposed

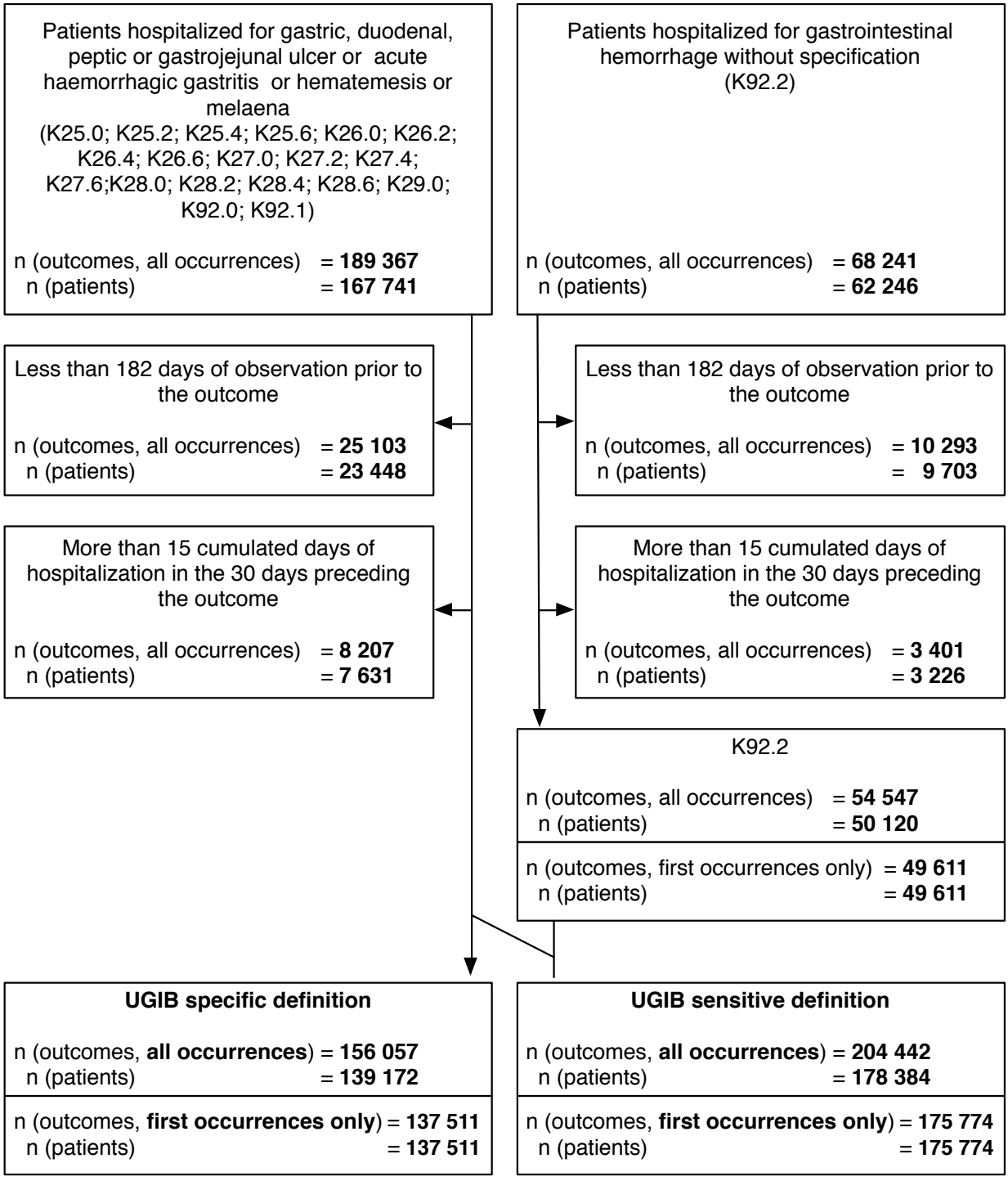
	population. In the pRR calculation the proportion of unexposed persons in the case group and in the population are not disregarded. In addition, CP allows the measure of relative risks based on per-patient exposure or per patient-time exposure. A total of 80 CP variants were executed using an in-house program developed in R. A part of the analyses was replicated in SAS® to ensure internal validity. (III) To assess the ability of the methods and their variants to distinguish between positive and negative controls, sensitivity, specificity and the area under the receiver operating characteristic curve (AUC) were estimated. Assuming that negative control log relative risk was zero, accuracy of the magnitude of the effect estimated was assessed using mean square error (MSE) and coverage probability calculation. (IV) Considering the estimates from the negative controls, for which a theoretical value of 1 was expected, we observed how often $p < 0.05$ while the null hypothesis was true, and we used the EmpiricalCalibration R package to fit distribution to the effect estimates, modeling the distribution of the residual bias under the null. Estimated parameters of this "empirical null distribution" was then used to compute "calibrated" p-values, taking into account random (as the traditional *p*-value does) and systematic error (i.e. the background noise) inherent to the application of a design variant to the SNDS.

PARTICIPANT FLOW


Patients hospitalized for a toxic liver disease with necrosis or hepatitis or acute hepatitis or for acute or subacute hepatic failure (K71.1; K71.2; K71.6; K72.0)
n (outcomes, all occurrences) = 36 081
n (patients) = 30 683
Patients hospitalized for a toxic liver disease without specification (K71.9)
n (outcomes, all occurrences) = 1 189
n (patients) = 1 145
Associated, related or main diagnosis corresponding to Z94.4 in the 182 days prior to the outcome
n (outcomes, all occurrences) = 348
n (patients) = 279
Associated, related or main diagnosis corresponding to Z94.4 in the 182 days prior to the outcome
n (outcomes, all occurrences) = 9
n (patients) = 7
Previous hospitalization end-date between the 1st and the 30th day prior to the outcome
n (outcomes, all occurrences) = 11 604
n (patients) = 11 223
Previous hospitalization end-date between the 1st and the 30th day prior to the outcome
n (outcomes, all occurrences) = 296
n (patients) = 295
Previous hospitalization end-date on the same day as the outcome with a corresponding start-date preceding the outcome by more than 7 days
n (outcomes, all occurrences) = 524
n (patients) = 523
Previous hospitalization end-date in the first day prior to the outcome with a corresponding start-date preceding the outcome by more than 7 days
n (outcomes, all occurrences) = 7
n (patients) = 7
Aggregation of concomitant hospitalizations (± 0 days)
Less than 182 days of observation prior to the outcome
n (outcomes, all occurrences) = 3 206
n (patients) = 3 070
Less than 182 days of observation prior to the outcome
n (outcomes, all occurrences) = 153
n (patients) = 150
Associated, related or main diagnosis corresponding to: B18; B24; C; F10; G31; I50; I81; I85; K70; K73; K74; K75.4; K76; K80; K83; R18; Z95; T86.4 in the 182 days prior to the outcome or during the hospitalization of interest
n (outcomes, all occurrences) = 13 148
n (patients) = 11 674
Associated, related or main diagnosis corresponding to: B18; B24; C; F10; G31; I50; I81; I85; K70; K73; K74; K75.4; K76; K80; K83; R18; Z95; T86.4 in the 182 days prior to the outcome or during the hospitalization of interest
n (outcomes, all occurrences) = 261
n (patients) = 257
Associated or main diagnosis corresponding to: B15; B16; B17; B19; B25.1; K77; O26.6; S36.1; T36-T65; during the hospitalization of interest
n (outcomes, all occurrences) = 1 521
n (patients) = 1 517
Associated or main diagnosis corresponding to: B15; B16; B17; B19; B25.1; K77; O26.6; S36.1; T36-T65; during the hospitalization of interest
n (outcomes, all occurrences) = 94
n (patients) = 94
K71.9
n (outcomes, all occurrences) = 368
n (patients) = 363
n (outcomes, first occurrences only) = 362
n (patients) = 362
ALI specific definition
n (outcomes, all occurrences) = 5 225
n (patients) = 5 152
n (outcomes, first occurrences only) = 5 132
n (patients) = 5 132
ALI sensitive definition
n (outcomes, all occurrences) = 5 580
n (patients) = 5 495
n (outcomes, first occurrences only) = 5 471
n (patients) = 5 471

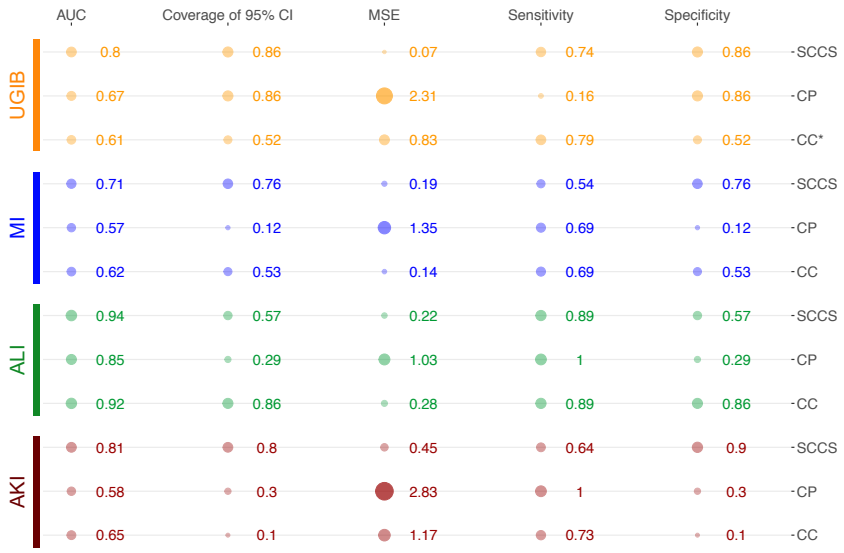

Patients hospitalized for an acute kidney failure with tubular or cortical or medullary necrosis (N17.0; N17.1; N17.2)
n (outcomes, all occurrences) = 28 487
n (patients) = 26 817
Patients hospitalized for an acute kidney failure without specification (N17.8; N17.9. N19)
n (outcomes, all occurrences) = 176 732
n (patients) = 152 094
Less than 182 days of observation prior to the outcome
n (outcomes, all occurrences) = 3 070
n (patients) = 2 875
Less than 182 days of observation prior to the outcome
n (outcomes, all occurrences) = 26 608
n (patients) = 24 156
Associated, related or primary diagnosis corresponding to E14.2; N14.3; N18; N26; N28.0; N28.1; N99; O90.4; P96.0; Q61; T86.1; Z90.5 in the 182 days prior to the outcome or during the hospitalization of interest
n (outcomes, all occurrences) = 11 337
n (patients) = 10 549
Associated, related or primary diagnosis corresponding to E14.2; N14.3; N18; N26; N28.0; N28.1; N99; O90.4; P96.0; Q61; T86.1; Z90.5 in the 182 days prior to the outcome or during the hospitalization of interest
n (outcomes, all occurrences) = 66 049
n (patients) = 55 434
Associated, related or primary diagnosis corresponding to Z94.0 in the 182 days prior to the outcome
n (outcomes, all occurrences) = 96
n (patients) = 89
Associated, related or primary diagnosis corresponding to Z94.0 in the 182 days prior to the outcome
n (outcomes, all occurrences) = 1 016
n (patients) = 854
Associated or primary diagnosis corresponding to T56; T57; T62.0 during the hospitalization of interest
n (outcomes, all occurrences) = 16
n (patients) = 16
Associated or primary diagnosis corresponding to T56; T57; T62.0 during the hospitalization of interest
n (outcomes, all occurrences) = 41
n (patients) = 40
More than 15 cumulated days of hospitalization in the 30 days preceding the outcome
n (outcomes, all occurrences) = 1 335
n (patients) = 1 301
More than 15 cumulated days of hospitalization in the 30 days preceding the outcome
n (outcomes, all occurrences) = 4 976
n (patients) = 4 782
N17.8; N17.9; N19
n (outcomes, all occurrences) = 78 042
n (patients) = 72 738
n (outcomes, first occurrences only) = 71 659
n (patients) = 71 659
KI specific definition
n (outcomes, all occurrences) = 12 633
n (patients) = 12 317
n (outcomes, first occurrences only) = 12 285
n (patients) = 12 285
KI sensitive definition
n (outcomes, all occurrences) = 89 186
n (patients) = 82 610
n (outcomes, first occurrences only) = 81 357
n (patients) = 81 357


Patients hospitalized for an acute transmural or subendocardial myocardial infarction or without precision (I21.0; I21.1; I21.2; I21.3; I21.4; I21.9)
n (outcomes, all occurrences) = 425 609
n (patients) = 361 007
Patients hospitalized for a unstable angina (I20.0)
n (outcomes, all occurrences) = 452 472
n (patients) = 362 481
Less than 182 days of observation prior to the outcome
n (outcomes, all occurrences) = 60 687
n (patients) = 53 010
Less than 182 days of observation prior to the outcome
n (outcomes, all occurrences) = 59 592
n (patients) = 51 539
More than 15 cumulated days of hospitalization in the 30 days preceding the outcome
n (outcomes, all occurrences) = 10 813
n (patients) = 9 799
More than 15 cumulated days of hospitalization in the 30 days preceding the outcome
n (outcomes, all occurrences) = 7 740
n (patients) = 6 663
I20.0
n (outcomes, all occurrences) = 385 140
n (patients) = 311 410
n (outcomes, first occurrences only) = 305 910
n (patients) = 305 910
MI narrow definition (MI1)
n (outcomes, all occurrences) = 354 109
n (patients) = 304 369
n (outcomes, first occurrences only) = 302 034
n (patients) = 302 034
MI broad definition (MItot)
n (outcomes, all occurrences) = 717 920
n (patients) = 558 538
n (outcomes, first occurrences only) = 548 160
n (patients) = 548 160



RECRUITMENT	Début des inclusions : 01/01/2019 Durée de la période d'inclusion : 6 ans (date de fin des inclusions : 31/12/2014) Durée de participation de chaque patient : entre 182 jours et 6 ans Date de dernière visite du dernier patient : NA Durée totale de la recherche : 6 ans
BASELINE DATA	*Baseline* ***demographic and clinical characteristics*** *of each group.* - ALI

	Near 60% of patients were female with a median age of 55 years old (54 for the sensitive definition). Almost 13% of the population presented at least one long term disease registration (*Affection longue durée* - ALD) prior to index date. - AKI Almost 59% of patients were male (56% for the sensitive definition) with a median age of respectively 69 years old for the specific definition and 75 for the sensitive one. Almost 40% of the specific population and 44% of the sensitive one presented at least one long term disease registration (*Affection longue durée* - ALD) prior to index date. No significant differences were observed in the sampled population. - MI Near 66% of patients were male with a median age of 70 years old. Almost 22% of the population presented at least one long term disease registration (*Affection longue durée* - ALD) prior to index date (20.5% for the sensitive definition). No significant differences were observed in the sampled population. - UGIB Almost 57% of patients were male with a median age of 72 years old. Near 34% of the population presented at least one long term disease registration (*Affection longue durée* - ALD) prior to index date. No significant differences were observed in the sampled population.
TRIAL INTERRUPTION	*Was the **trial interrupted**?* No
OUTCOMES AND ESTIMATION	**Overall results** Considering all the design variants executed in the sampled population, SCCS globally showed the best performances across all the outcomes. Focusing on HOI specific definitions, best SCCS generated 0.7≤AUC≤0.94 and 0.07≤MSE≤0.45. CP and CC presented similar AUC (ALI: 0.85 and 0.92; MI: 0.57 and 0.62; AKI: 0.58 and 0.65; UGIB: 0.67 and 0.61) whereas MSE were much more important in CP (ALI: 1.03 *vs.* 0.28; MI: 1.35 *vs.* 0.14; AKI: 2.83 *vs.* 1.17; UGIB: 2.31 *vs.* 0.83)



For a same outcome definition, several SCCS variants showed very closed results. Design variants presented in the following section were chosen based on their overall performances in the sampled populations, when possible across both specific and sensitive definitions. and executed in the unsampled populations.

ALI

SCCS designs considering the first occurrence of the outcome, the length of the period of dispensing as the risk window and adjusting for multiple drugs presented optimum performances for the specific and the sensitive definitions with respectively AUC=0.93 and 0.92, MSE=0.22 and 0.19 and coverage probability = 86%.

MI

In the specific unsampled MI population, SCCS designs considering all occurrence of the outcome, the 30 first days following the dispensing as the risk window and adjusting for age and seasonality presented optimum performances with AUC=0.76, MSE=0.146 and coverage probability=50%.

In the unsampled sensitive MI population, SCCS designs considering the first occurrence of the outcome, the 30 first days following the dispensing as the risk window and adjusting for age and seasonality presented optimum performances with AUC=0.81, MSE=0.19 and coverage probability=53%.

AKI

The SCCS design variant considering the first occurrence of the outcome, the period of dispensation as the risk window and adjusting for age and multiple drugs seemed to be optimum in the AKI unsampled population for both specific and sensitive definition with respectively AUC=0.84 and 0.80, MSE=0.191 and 0.291 and coverage probability = 70% and 65%.

UGIB

The SCCS design variant considering the first occurrence of the outcome, the 30 first days following the dispensing as the risk window and adjusting for multiple drugs seemed to be optimum in the UGIB

	unsampled population for both specific and sensitive definition with respectively AUC=0.84 and 0.85, MSE=0.14 and coverage probability = 75% and 78%.
ANCILLARY ANALYSIS	In order to better understand the influence of the different SCCS parameters, univariate logistic analyses were computed to screen for the ones with major impact, i.e., those resulting in a high AUC. For each HOI definition, the thresholds distinguishing high from low AUC was selected as the value above which were the 30% best AUC **ALI** Parameter of major importance for drug-related ALI assessment seemed to be the risk window, which should be set to the length of the period of dispensing. **MI** Parameter of major importance for drug-related MI assessment seemed to be the risk window, which should be set to the 30 first days following the dispensing. For both specific and sensitive definition SCCS variants adjusting for multiple drugs use, presented lower AUC but higher coverage probability. For the sensitive definition better AUC were observed for SCCS variants only considering the first occurrence of the outcome without any pre-exposure window. **AKI** Parameter of major importance for drug-related AKI assessment for both specific and sensitive seemed to be multiple drug adjustment. Variants without pre-exposure windows showed the highest AUC. **UGIB** Parameters of major importance for drug-related UGIB assessment for both specific and sensitive seemed to be multiple drug adjustment and restricting the outcome to consider to their first occurrences. For UGIB specific definition, setting the risk windows to the 30 first days following the dispensing seemed also have a major impact on AUC.
ADVERSE EVENTS	*All **important adverse events** or side effects in each intervention group.* NA
TRIAL TERMINATION	*Study **terminated prematurely** Y/N* *State reason for premature termination* No

DISCUSSION AND INTERPRETATION OF STUDY RESULTS	***Interpretation of trial results :*** Across all the outcomes, the self-controlled case series showed better results than CC and CP in terms of discrimination and accuracy of point estimates in this large-scale assessment in the SNDS. Except for MI, multiple drug adjustment seems to have a positive impact on the discriminative ability of SCCS and coverage probabilities. The restriction of the outcome occurrences to consider to the first one also seemed to be a key parameter. Optimal risk window appeared to strongly depend on the outcome of interest. For ALI and AKI, the use of a risk window corresponding to the overall period covered by the drug dispensing showed better results. For MI and UGIB a 30-day risk window starting at exposure enhanced performances. These discrepancies may be explained by outcome mechanisms and drug controls natures. For example, inclusion criteria were very restrictive for ALI. Thus, most of the outcome captured result from acute hepatocellular toxicity, which may occur only few days after the treatment initiation. Since a large part of ALI drug controls were non-chronic drugs, using a fixed period of 30 days led to consider non-exposed extra time that is less at risk, and then distort the estimate. In UGIB, the better performances observed restricting the risk window to the 30 first days from dispensing may be related to the exclusion of non-specific bleeding that happens long after treatment initiation and that is unrelated to the drugs of interest, or to a depletion of susceptibles. Obviously, the designs identified in this work as optimum could be further improved, but the empirical assessment showed that performances of SCCS as it is, with carefully selected parameters, were decent enough for the identification of drugs associated with ALI, AKI, MI and UGIB. False positives revealed that some biases remained, especially protopathic bias and confounding by indication. However, most of the time, a clinical point of view allowed discrimination between true and false positives. Besides, some positive controls were not detected during the experiment, sometimes showing no effect at all, or positive but non-significant effect. The positive but non-significant effect can be reasonably attributed to a lack of power resulting from a small number of outcomes or a weak exposure. One wonders about the real impact of such a drug in the overall population. Furthermore, since pharmacoepidemiology captures the actual effect of a drug in real life conditions, the absence of association can reasonably suggest that the event of interest is not a safety issue for the considered medicine in the day to day practice. This could be the consequence of the actual innocuity of the drug, or of confounding by (contra)indication, which would mean that the existing risk is correctly managed. All in all, these works showed that SNDS is perfectly suitable to generate drug safety alerts in an accurate manner. Thus, a pertinent interpretation by health specialists of the estimates generated by the previously highlighted reference designs in the SNDS should provide valuable input for drug safety alert generations at a national level. Such method can be used to validate a signal generated through another source and quantify the potential risk, or to screen routinely a large set of newly marketed drugs. To do so, reference methods could first be applied across all the drugs of a SNDS extraction. Risk already documented would be ruled out, and emerging alerts carefully studied to distinguish between biased, potential, and confirmed alerts. Second, newly marketed or suspected drugs could be screened on a yearly basis. This approach extend to other outcomes of interest for drug safety could

	consist in substantial progress in pharmacovigilance in France.