Alert generation using the case-population approach in the French Nationwide Healthcare Database (SNDS): the ALCAPONE project

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Background

- SNDS is the French Nationwide Healthcare System Database covering about 99% of the French population; EGB is its1/97th random permanent representative sample.
- ALCAPONE is a project aiming to : 1) develop the case population design on SNDS for drug safety signal generation; 2) compare the performance of the case-population design with self-controlled case series and case-control design for signal generation; 3) identify the best design for a given health outcome of interest.

Methods

Study design

✓ OMOP reference set
- 4 health outcomes of interest
  - Acute liver injury (ALI)
  - Acute kidney injury (KI)
  - Myocardial infarction (MI)
  - Upper gastrointestinal bleeding (UGIB)
- Drug controls
  - Positive controls (CTR+) = associated with the outcome of interest (RR>1)
  - Negative controls (CTR-) = no associated with the outcome of interest (RR≈1)

✓ Historical data
- From EGB (feasibility study) and SNDS (final study) between 2009 and 2014

Project stages

1. Case-based patients extraction and selection of the detectable drug controls
   - Extraction and data management of 4 sub-populations : ALI, MI, KI, UGIB according to a broad and a narrow definition
   - Selection of the drugs available and reimbursed in the French community pharmacies among the OMOP Reference set
   - Calculation of the minimum detectable relative risk (MDRR) of each drug-outcome pair
   - Selection of the controls with MDRR ≤ 1,25.

➔ Generation of 4 sub-study databases composed of the cases extracted for a health outcome of interest and the corresponding drug controls.

2. Drug-outcome pairs detection
   - Generation of a measure of association for each drug-outcome pair
     - *Via* 3 study designs:
       - case-control (OHDSI package)
       - self-controlled case series (OHDSI package)
       - case-population.
     - Each study design is repeated according to different settings forming a variant:
       - Case-control: number of controls per case, matching strategy…
       - Self-controlled case series: adjustment strategy, pre-exposure window…
       - Case-population: exposure window, exclusion period…

➔ Generation of one measure of association by drug-outcome pair and design variant.

3. Comparison of design and design variants performances
   - Discriminating power
     - Number of detected CTR+ et CTR- ➔ Area under the ROC curve
   - Accuracy of the measure of association (for CTR- only)
     - $Bias = mean[\log(RR_{est}) - \log(RR_{true})]$
     - $MSE = mean[[\log(RR_{est}) - \log(RR_{true})]^2]$
     - Coverage probability: frequency over replications that the confidence interval contains the true value

➔ Selection of the best design variant for each health outcome of interest.

➔ Calibration of the selected design variant using the distribution of the CTR-.

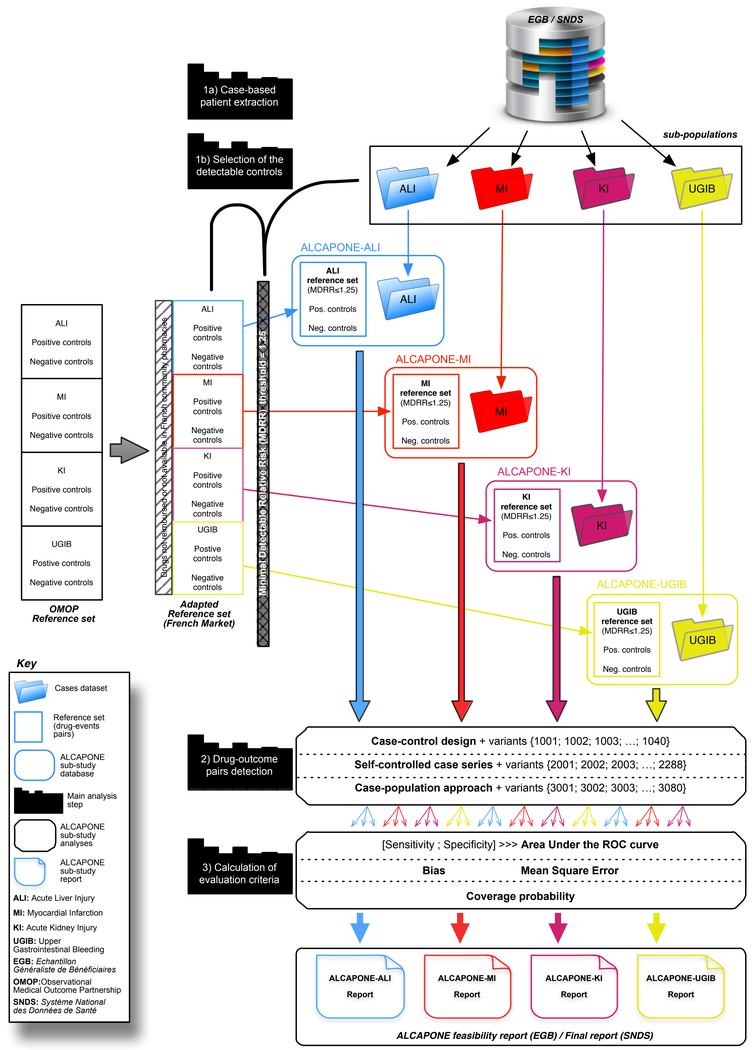

Figure 1. *Overall ALCAPONE process*

Results

Feasibility study

- Corresponds to the application of the 1st stage of the process to the EGB.
- The number of extracted cases in the EGB is displayed in Table 1.
- On the Table 2. the left part shows the number of controls with MDRR≤1.25 in a database of the OMOP experiment. The right side displays the results of the feasibility study in the EGB and its extrapolation to the SNDS by health outcome of interest.

Table 1. *Outcomes extracted from EGB and number of patients by health outcome of interest*

		ALI		MI		KI		UGIB	
		Narrow Def.	Broad Def.	Narrow Def.	Broad Def.	Narrow Def.	Broad Def.	Narrow Def.	Broad Def.
EGB (observed)	n (outcomes)	33	40	3 202	6 334	94	758	1 390	1 771
	n (patients)	32	40	2 757	4 962	93	712	1 213	1 522

Table 2. *Number of positive and negative controls (CTR+ and CTR-) by health outcome of interest, present in the OMOP experiment, available in the French market, detectable in EGB and expected in SNDS*

		OMOP Reference set	OMOP Experiment[1] Number of detectable controls[2]		French market Reference set	EGB Number of detectable controls[2]		SNDS Expected number of detectable controls[2]	
			Narrow definition	Broad definition		Narrow definition	Broad definition	Narrow definition	Broad definition
ALI	CTR+	*81*	*57*	*63*	56	0	0	15	18
	CTR-	*37*	*32*	*32*	19	0	0	1	2
MI	CTR+	*36*	*26*	*33*	26	3	5	23	23
	CTR-	*66*	*37*	*46*	37	1	5	29	31
KI	CTR+	*24*	*19*	-	19	0	3	11	18
	CTR-	*64*	*34*	-	32	0	0	5	16
UGIB	CTR+	*24*	*24*	*22*	19	5	7	18	19
	CTR-	*66*	*53*	*49*	38	1	1	30	31

[1] Results from the MarketScan Commercial Claims and Encounters database [2] Drug controls with MDRR≤1.25

- The low number of detectable controls in ALI and KI could result from the small size of the extraction and the random error: to be considered as detectable in the SNDS, only 2 exposed cases are required in the EGB.
- *SelfControlledCaseSeries* and *CaseControl* OHDSI R packages have been successfully implemented in EGB.
- *CasePopulation* package development is currently ongoing.

Final study

- Cases have been extracted from SNDS (Table 3.).
- Data management and power calculation (MDRR) are currently in process.

Table 3. *Outcomes extracted from SNDS and number of patients by health outcome of interest*

		ALI		MI		KI		UGIB	
		Narrow Def.	Broad Def.	Narrow Def.	Broad Def.	Narrow Def.	Broad Def.	Narrow Def.	Broad Def.
SNDS (observed)	n (outcomes)	5 232	5 588	354 109	717 920	12 633	89 186	156 057	204 442
	n (patients)	5 154	5 497	304 369	558 538	12 317	82 610	139 172	178 384

Conclusions

- Extraction process and data management stage ensure the generation of a database suitable for the utilization of OHDSI R packages.
- EGB is not powerful enough to detect associations ≤ 1.25 among a sufficient number of drug-outcome pairs.
- SNDS seems to have a sufficient size to implement the whole ALCAPONE process.
- Once selected and calibrated, the reference method will be used to detect (1 suspected drug- several outcomes) and validate (1 drug-1 outcome) pharmacovigilance alerts.

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2018 European OHDSI Symposium, March 23th, Rotterdam, Netherlands

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