

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in medical practice for treating pain, inflammation and degenerative joint diseases (for instance, arthritis). The use of traditional NSAIDs (tNSAIDs), however, is associated with an increased risk of minor and serious gastrointestinal (GI) events. It is estimated that in the European Union thousands of gastrointestinal complications are caused by the use of NSAIDs. A new class of NSAIDs, the “Coxibs”, was developed specifically to minimize the risk of gastrointestinal events. Since their introduction, however, the use of these newer NSAIDs raised concerns as they may increase the risk of cardiovascular events (CV), among which myocardial infarction and ischemic stroke. In this context, the risk of gastrointestinal events has to be balanced against the risk of cardiovascular events. Both risks may differ in a single subject and for over 40 different NSAIDs that are available in the EU. For children the risk of asthmatic exacerbations, renal and hepatic failure, anaphylaxis, Reye’s and Steven Johnsons’ syndromes are also of concern.

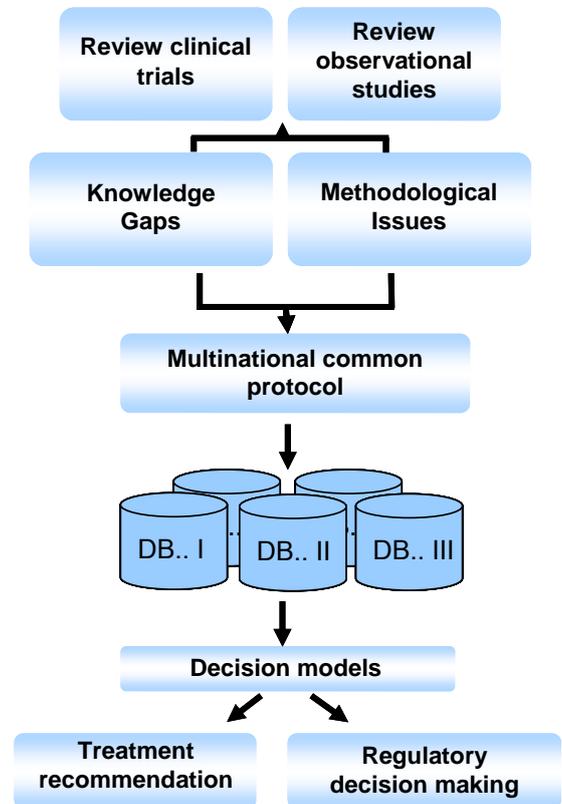
The **SOS** project aims to assess and compare the risk of cardiovascular and gastrointestinal events among NSAIDs users, with the ultimate goal to differentiate between NSAIDs and thereby providing decision models to clinicians and regulatory authorities, such as medicines agencies to guide the selection process of NSAIDs in clinical practice and minimize drug related harm.

SOS combines data from different countries, bringing into the research the heterogeneity and increased sample size which are important for risk assessment and comparison of the different NSAIDs in subgroups such as adults and children.

The **key challenges** to accomplish the **SOS** objectives are:

- To systematically review published **studies and meta-analyses of clinical trials and observational studies** addressing either GI or CV risk of tNSAIDs and coxibs to extract event rates, risk factors and relative effect sizes
- To identify **methodological issues** in available clinical trials and observational studies and to summarize **knowledge gaps**, which need to be resolved to take regulatory or treatment decisions
- To design and conduct **common-protocol multi-country database studies** to address the knowledge gaps and methodological issues of previous studies, including the dose and duration-response relationship, aspects of timing of risk and comorbidity and comedication. To provide the risk functions of outcomes per NSAID and by dose and duration

- To develop and run **statistical and decision models** that will allow for **clinical treatment decisions** based on balancing the relative GI and CV safety of coxibs and tNSAIDs.



The **SOS** project has created an international network of experts and databases comprising health care data of more than 35 million persons from EU countries for the conduct of the largest study on this topic that has ever been performed. The combination of the databases will not only provide a larger sample size but will allow also to profit from the heterogeneity in prescription patterns that exist between Southern and Northern Europe. By using the databases to address methodological issues in previous studies the project will not only estimate the risk of GI and CV for all NSAIDs, but it will also be able to investigate whether contrasting results in previous studies may be explained by methodological issues. Moreover it will enable the risk assessment in vulnerable subgroups such as children and the elderly.

SOS is carried out by an interdisciplinary team of researchers carefully selected by their scientific expertise.

- Erasmus University Medical Center, Netherlands. *Project Coordinator.*
- Fundació IMIM, Spain.
- University of Nottingham, UK.
- Università di Milano-Bicocca, Italy.
- Research Triangle Institute, Spain (USA).
- Universitaet Bremen, Germany.
- The Research Institute of the McGill University Health Centre, Canada.
- Azienda Ospedaliera di Padova, Italy.
- Pharmo Coöperation UA, Netherlands.
- Université Victor-Segalen Bordeaux II, France.
- Azienda Sanitaria Locale della provincia di Cremona, Italy.
- The Societa' Servizi Telematici, Italy.