**Work Package 1: Real-world evidence for economic evaluation of medical devices: methodological challenges and applications**

Research Protocol of Task 1

A comprehensive assessment of existing sources of real world evidence

on medical devices in Europe

Project Lead: UB

Involved: all partners

# **Project: aims**

The aim of the project is to provide a comprehensive assessment of possible sources of real world evidence (RWE) for medical devices in European countries (e.g. registries, administrative data).

This phase includes the analytic search for consolidated data collection activities at the European level, followed by a systematic search in the countries included in the COMED project (Italy, UK, Netherlands, Switzerland, Germany and Hungary) and beyond. This mapping exercise will also include the possibility that sources of real world data (RWD) are collected at the sub-national or cross-national level by scientific networks (e.g. scientific societies, hospital networks, etc.). Finally, and in order to ensure relevance of our findings beyond the countries included in the COMED project, we will make an effort to enlarge the scope of our mapping and include relevant international databases at pan-European level (i.e. EU registries for medical devices).

# **Research Protocol**

This research protocol provides the procedural framework for a stepwise development of Task 1 and elucidates the steps to implement the task.

## **Sources of RWD**

The project aims to inform on existence of available RWD and propose methodologies to analyze cost and outcome data of medical devices derived from these sources. As stated above, the project’s work consists in an analytic search for consolidated data collection activities at the European level, and in the countries that are part of the COMED Project and others. The choice of which sources of RWD are best suited for this task was taken accordingly. We selected those sources generally considered primary sources of RWD (Garrison et al., 2007; Makady et al., 2017[[1]](#footnote-1)), and among them, those that will facilitate the use of RWD for HTA across Europe, and therefore that are more commonly available and comparable across countries. Finally, the RWE selection also balanced the trade-off between including as many sources as possible and assuring the feasibility of the task according to the time and established person-months allocated to Task 1 in the COMED project. We therefore focused on the following RWD sources:

**Selected sources of RWD**

|  |
| --- |
| Administrative Data |
| Registry Data |
| Other observational Study |
| Other (open category in case of some specific source of data considered relevant to the aim of the task and not covered in previous categories) |

**Timeframe**

Given that one of the aims of the project is to develop methods to be used by policymakers to set up structured collection of RWD, we decided to include only studies and sources of RWD still ongoing or finished no more than five years ago. The rationale for this choice is to include only sources that may be relevant and usable today for economic evaluations, in agreement with the objectives of the project.

## **Case studies**

The mapping of RWD will focus on three case studies, selected in order to be relevant to the general aim of project, hence policy-relevant, and cover a spectrum of cases as wide as possible in terms of the epidemiology of diseases, demographic trends (e.g. population ageing) and maturity and type of technologies.

**Selected case studies**

|  |  |  |  |
| --- | --- | --- | --- |
| **n** | **Disease** | **Procedure** | **Medical Device** |
| 1 | Arthrosis of the knee/hip | Knee/hip replacement or revision | Knee/hip endoprosthesis |
| 2 |  | Robot surgery | DaVinci robotic surgery system |
| 3 | Cardiovascular disease | [Trans-Catheter Valve Treatment](https://www.escardio.org/Research/Registries-&-surveys/Observational-research-programme/TransCatheter-Valve-Treatment-TCVT-Registry) | Trans-catheter Aortic Valve Implantation (TAVI) Trans-catheter Mitral Valve Repair (TMVR) |

## **Research strategy**

For each case study, sources of RWD data will be searched through a combination of research strategies:

* 1. Screening of national relevant sources (e.g. website of Ministry of Health, national institutions, research bodies), both in local language and English.
  2. Systematic search on PubMed and Scholar using a set of key words common to all partners.

**Key words** are defined for each case study and adapted to each research context (i.e. country). The general key words combination will consist in:

(Sources of RWD) AND (Disease OR Procedure OR Medical Device) AND (Country)

An example for the case of arthroplasty is give in Figure 1 and Appendix A1 includes key words for each case study.

**Figure 1.** PubMed key words for case study 1 arthroplasty/hip and knee arthrosis/endoprosthesis

((Regist\* OR "Observational Study" OR "Observational Studies" OR "Administrative data")

Case-specific

AND (("Arthrosis" OR replacement OR revision OR endoprosthesis) AND (knee\* OR hip))

Common to all searches

AND (Italy OR Italia))

Country-specific

**Exclusion criteria**

The following exclusion criteria are applied to screen the studies collected in the systematic search.

* Studies using non RWD (e.g. randomized control trials) are not included;
* Studies using sources of data not listed among the selected sources of RWD are not included;
* Studies using RWD included in the list of types of selected sources, but produced involving only one research unit (e.g. single hospital, single research center, patients of one surgeon) are to be excluded. This exclusion criterion has two exceptions: 1) It does not apply to case study 2 (robotic surgery), because less evidence is available and therefore even small studies can be relevant. 2) For case studies 1 and 3, if a single-center study is considered particularly relevant (e.g. because a large number of patients is included, because it is longitudinal, because it includes data not available elsewhere) it will be included and a justification provided.
* Non empirical studies (e.g. literature reviews and meta-analyses, commentaries, etc) are excluded;
* Studies not set in the country of interest are excluded;
* Studies not ongoing and finished more than 5 years ago (2013) are excluded;
* Studies dealing with neither the disease or procedure or device of interest, are excluded.

**Screening and selection** of studies will be illustrated through an adapted version of the PRISMA flowchart (see Appendix A2). The number of articles that will be excluded will be reported by the abovementioned exclusion criteria, grouped in five categories “type of data source” (including non-RWD, RWD not selected for this study, RWD included in the list of sources but produced in a single-unit center (unless any exception)), “non-empirical study”, “country of setting”, “obsolete source of RWD (5+ years)” and “study subject”.

The remaining two strategies consist in seeking advice from key players in the field of the device, procedure or disease:

1. Ask manufacturer (to be managed discretionally)
2. Ask opinion leaders (to be managed discretionally)

# **The Template for Mapping RWD**

When the sources of data are identified, information on each dataset need to be entered in the **template.** The template consists of a large table presenting multiple columns for describing each dataset across multiple fields. These are:

* RWD Source features:
  + Name of the source
  + Data provider/initiator
  + Type of study
  + Inclusion-approach
  + Data Accessibility
  + Aggregation level
  + Coverage (geographical)
  + Whether data collection is ongoing
  + Coverage period
  + Completeness
  + Sample size
* RWD Source Content:
  + Socio-Demographic data
  + Clinical/Epidemiological data
  + Economic outcomes
  + Health outcomes
  + Type of DIAGNOSIS classification
  + Type of PROCEDURE classification
  + Medical device traceable
  + Comparator/ comparison
  + Other variables
* Comments
* Reference/link to the source

Each case study will have its own template, each row of the template will include information on each source of RWD available for the case study.

**Guideline to the Template**

The template consists of an excel document including 4 sheets:

* “Template”: includes the actual table to fill in.
* “Guideline to template”: explains the content of the template: what each column means, the expected type of answer (open/closed, single choice, multiple choice), and provides an example for each cell field.
* “Definition”: offers a further clarification of terms (e.g. observational study vs registry)
* “List of variables”: provides a list of answers for closed choice answers, and examples for open answers. NB: This sheet is a further tool to understand the template, closed answers will be automatically selected from the template, and open content answers need to be entered directly in the cells of the template. This list of variables has to be used to have a clearer insight.

Below some specific instructions are provided for those fields of the template that may require further clarification in order to produce homogeneous templates across countries:

* Sample size: please provide information on the latest available time, if possible by year, otherwise by the latest available interval time whatever it is.
* Open answers “which variables” for “Clinical/epidemiological Data”, “Resource Use” and “Health Outcomes”: if a dataset has a relatively extensive number of variables, do register the sub-categories with some examples of the variables that are collected within these sub-categories, and provide the total number of available variables if possible.

Example for clinical/epidemiological data: general information patient (e.g. height and weight, date of decease), Emergency care (e.g. date of diagnosis), Surgery (e.g. diagnosis and procedure), Complication, Discharge (e.g. date of discharge).

# **Appendix**

## **A1. PubMed key words for each case study**

Please do edit the last part “country” as appropriate.

**Case study 1**

((Regist\* OR "Observational Study" OR "Observational Studies" OR "Administrative Data”) AND ("Arthrosis" OR replacement OR revision OR endoprosthesis) AND (knee\* OR hip)) AND (country)

**Case study 2**

((Regist\* OR "Observational Study" OR "Observational Studies" OR "Administrative Data”) AND ("robotic surgery" or "robot surgery" or "robotic surgeries" OR “Da Vinci” OR “Davinci”)) AND (country)

**Case study 3**

((Regist\* OR "Observational Study" OR "Observational Studies" OR "Administrative Data”) AND ("TransCatheter Valve Treatment" OR “Transcatheter Aortic Valve Implantation” OR “TAVI” OR “Transcatheter Mitral Valve Repair” OR “TMVR”)) AND (country)

where *country* needs to be specified for each research setting

## **A2. PRISMA 2009 Flow Diagram**

Records identified through database searching (n = )

**Screening**

**Included**

**Eligibility**

**Identification**

Records screened after duplicates removed  
(n = )

Records excluded, with reasons\*

(n= )

Full-text articles assessed for eligibility (n = )

Full-text articles excluded, with reasons\*  
 (n= )

Studies included  
(n = )

RWD Source 1

RWD Source 2

RWD Source 3

…

RWD Source n

**Selected RWD**

\*provide as many of the five reasons listed in the text as needed (“type of RWD”, “non-empirical study”, “country of setting”, “obsolete source of RWD (5+ years)” and “study subject”)

The last stage (“Selected RWD”) present the selected sources of RWD individually or grouping them (e.g. 8 observational studies)

1. Garrison LP Jr, Neumann PJ, Erickson P, Marshall D, Mullins CD. Using real-world data for coverage and payment decisions: the ISPOR Real-World Data Task Force report. Value Health. 2007 Sep-Oct;10(5):326-35. Makady A, de Boer A, Hillege H, Klungel O, Goettsch W; (on behalf of GetReal Work Package 1). What Is Real-World Data? A Review of Definitions Based on Literature and Stakeholder Interviews. Value Health. 2017 Jul -Aug;20(7):858-865. doi: 10.1016/j.jval.2017.03.008 [↑](#footnote-ref-1)