

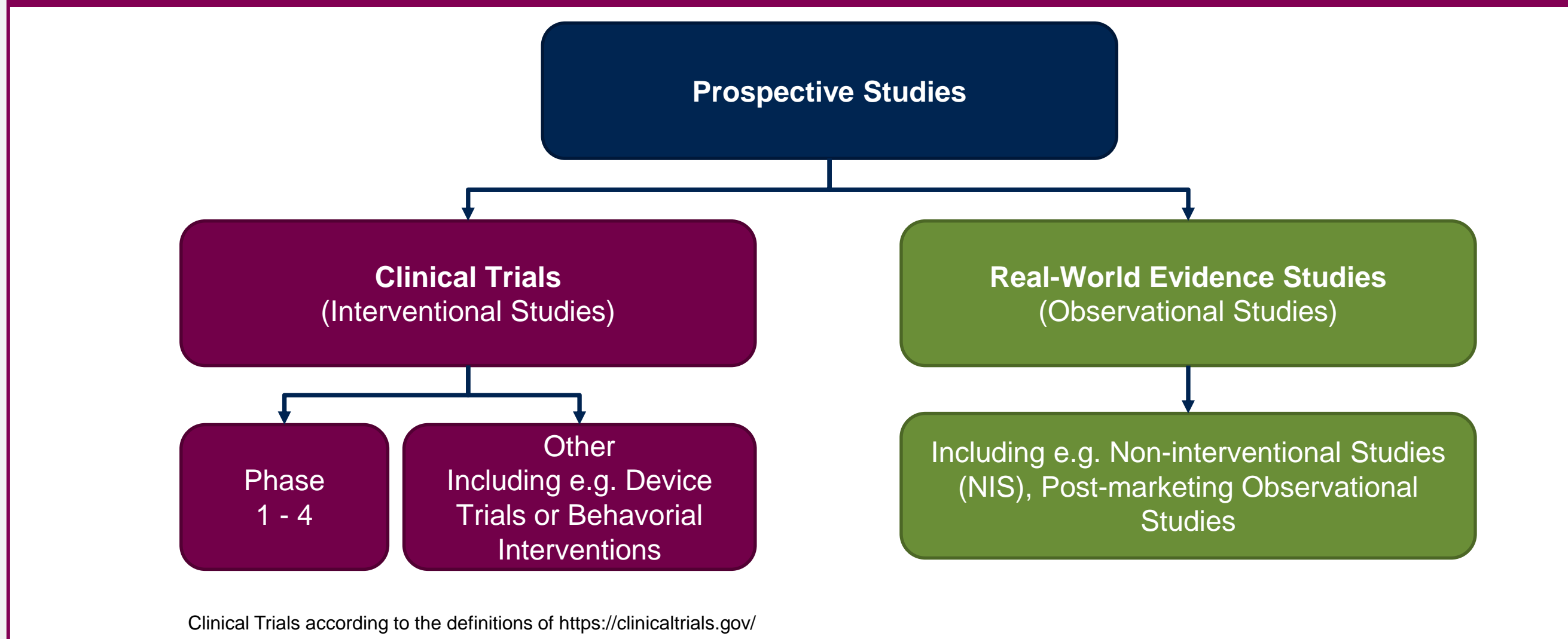
# LANDSCAPE ASSESSMENT OF PROSPECTIVE REAL-WORLD EVIDENCE STUDIES IN EUROPE

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## BACKGROUND

- Different definitions for prospective studies exist [1] and one of the most common definitions refers to the time of data collection.
- Prospective studies are mainly designed to collect data for future events in support of a specific research question.
- These studies can be subdivided into clinical trials (interventional studies) as well as real-world evidence (RWE) (observational) studies (see Figure 1).

Figure 1. Overview of Prospective Studies



- Clinical trials and RWE studies widely differ regarding their regulatory aspects as well as guidelines. While clinical trials are regulated very strictly across countries (e.g. Guideline for Good Clinical Practice (GCP)), less formalities exist for RWE studies.
- However, the importance of prospective RWE research is increasing also regarding the approval or post-approval safety processes as the focus of these studies is on the real-world treatment, more-representative patient populations and the analysis of current medical practice.

## OBJECTIVES

- The main aim of this analysis was to investigate the status quo of prospective RWE research in different European countries.
- Furthermore, these findings were put into context with the population size, pharmaceutical market value as well as regulatory aspects of the respective country.
- Additionally, this study aimed at identifying indications that were investigated in these studies.

## METHODS

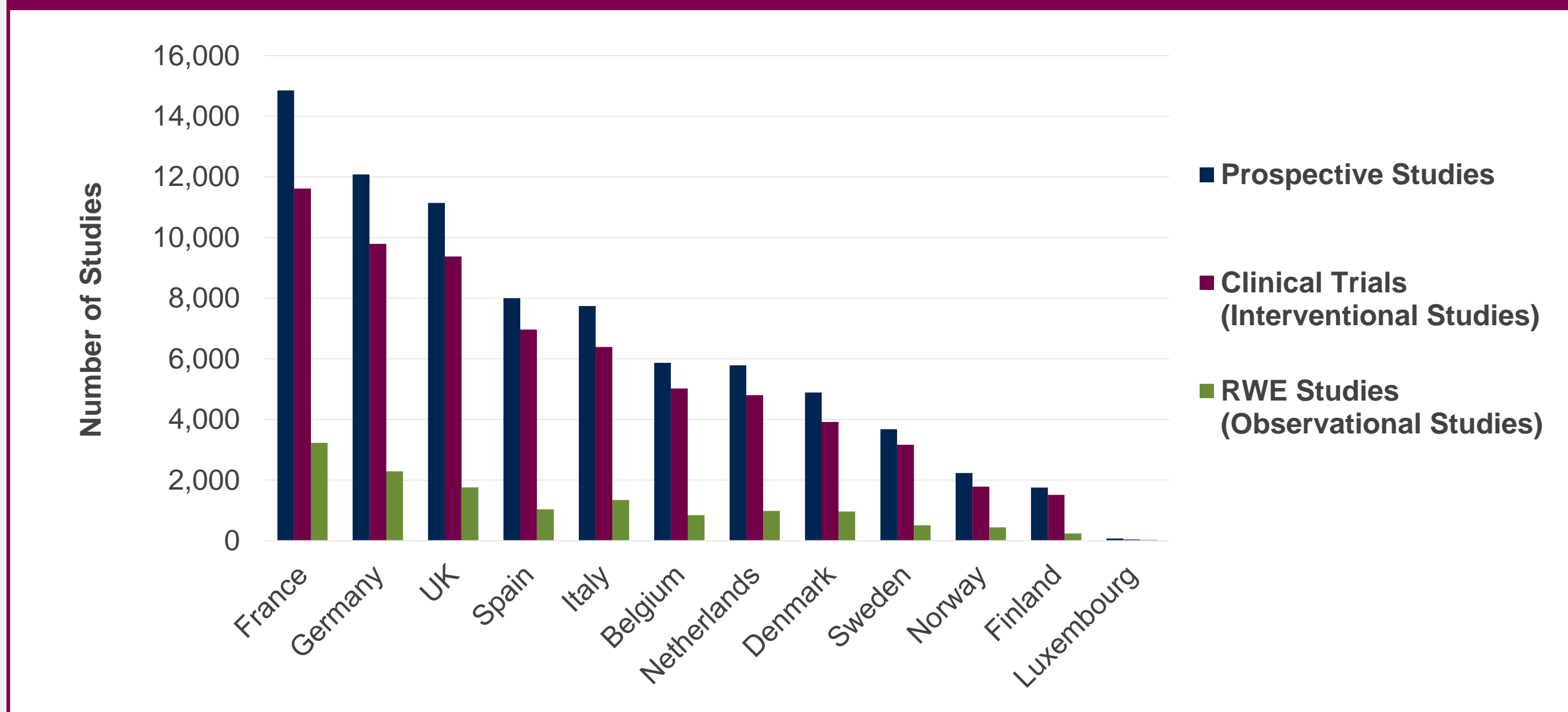
- A ClinicalTrials.gov database search was performed by applying the categories country, study type, and indication.
- All retrospective studies were excluded from the search, focusing on the study type "observational" with all recruitment conditions (e.g. not yet recruiting, recruiting, completed).
- Studies of the last ten years (06/2008 until 06/2018) were included, if they were conducted in the following European countries: Belgium, Denmark, Finland, France, Germany, Italy, Luxembourg, Netherlands, Norway, Spain, Sweden, and the United Kingdom (UK).
- The influence of the population and pharmaceutical market size as well as different regulatory requirements in each country were considered when interpreting the results.
- Furthermore, out of about 2,000 diseases the top five in the respective country were investigated.



## RESULTS

- The overall number of prospective studies was the highest in France (n=14,850), followed by Germany (12,083) and UK (n=11,141) (see Figure 2).
- The overall number of registered prospective RWE studies varied between the countries with France (n=3,232), Germany (n=2,290), UK (n=1,763), Italy (n=1,349), Spain (n=1,036), Netherlands (n=986), Denmark (n=971), Belgium (n=846), Sweden (n=514), Norway (n=447), Finland (n=240), and Luxembourg (n=33) (see Figure 2).

Figure 2. Number of Prospective Studies in 12 Selected European Countries Overall and Stratified by Study Type



- The countries could be categorized into two clusters with (1) the populous countries (Germany, France, UK, Italy and Spain) and (2) the Northern countries and Benelux.
- The proportion of RWE studies in relation to the number of overall prospective studies ranged from 13.0% in Spain to 41.3% in Luxembourg.
- This order of the two clusters changed when taking the population size of each investigated country [2] into account. Denmark, followed by Norway and Belgium had the highest proportion of RWE studies in relation to the population size (16.9 studies per 100,000 inhabitants in Denmark, 8.3 studies per 100,000 inhabitants in Norway, and 7.4 studies per 100,000 inhabitants in Belgium). Spain, Italy and the UK were at the rear ranks with 2.2 studies per 100,000 inhabitants in Spain, 2.3 studies per 100,000 inhabitants in Italy, and 2.6 studies per 100,000 inhabitants in the UK.
- Considering also the pharmaceutical market value of each country [3], which highly correlates with the population size ( $r=0.991$ ,  $p<0.001$ ), a similar ranking with the two clusters of countries could be observed (see Table 1).

Table 1. Prospective Studies and Pharmaceutical Market Value Stratified by European Country

Country	Total Population in Mio	Prospective Studies	Prospective RWE Studies	Number of Prospective Studies per 100,000 Inhabitants	Number of Prospective RWE Studies per 100,000 Inhabitants	Pharmaceutical Market Value in € Mio
Germany	82.3	12,083	2,290	14.7	2.8	30.0
UK	66.6	11,141	1,763	16.7	2.6	22.4
France	65.2	14,850	3,232	22.8	5.0	27.6
Italy	59.3	7,740	1,349	13.1	2.3	22.7
Spain	46.4	8,000	1,036	17.2	2.2	15.6
Netherlands	17.1	5,788	986	33.9	5.8	4.8
Belgium	11.5	5,870	846	51.1	7.4	4.7
Sweden	10.0	3,681	514	36.9	5.1	3.8
Denmark	5.8	4,892	971	85.0	16.9	2.3
Finland	5.5	1,758	240	31.7	4.3	2.2
Norway	5.4	22,38	447	41.8	8.3	1.6
Luxembourg	0.6	80	33	13.6	5.6	NA

Sources: Total Population in 2018 [2]; Prospective Studies from 2010 to 2018: <https://clinicaltrials.gov/>; Pharmaceutical Market Value at Ex-Factory Prices in 2015 [3]

- Regarding the regulatory requirements and guidelines of the European countries, some countries have very detailed regulations whereas others have hardly no legislation at all. In some countries an approval, registration and/or notification of the competent authority, ethic committee as well as data protection agency is required whereas in others, the official notification to these authorities is not necessary.
- Finland, Germany, and Italy were the countries with the highest number of institutions which have to be informed, followed by Belgium, Luxembourg, Spain, Sweden, and UK whereas Denmark, France, the Netherlands, and Norway had less regulations concerning the notification process.
- Concerning the investigated diseases in the RWE studies, vascular and heart diseases as well as respiratory tract diseases were among the top five diseases in most of the countries (see Figure 3).

Figure 3. Top 5 Diseases in Prospective RWE Studies Stratified by European Country

TOP	Belgium	Denmark	Finland	France	Germany	Italy	Luxembourg	Netherlands	Norway	Spain	Sweden	UK
TOP 1	Vascular Diseases (N=114)	Vascular Diseases (N=122)	Heart Diseases (N=35)	Vascular Diseases (N=398)	Heart Diseases (N=362)	Vascular Diseases (N=223)	Adenocarcinoma (N=5)	Heart Diseases (N=173)	Vascular Diseases (N=67)	Vascular Diseases (N=158)	Vascular Diseases (N=73)	Heart Diseases (N=232)
TOP 2	Heart Diseases (N=106)	Endocrine System Diseases (N=107)	Vascular Diseases (N=35)	Syndrome (N=308)	Vascular Diseases (N=348)	Heart Diseases (N=222)	Carcinoma (N=5)	Vascular Diseases (N=153)	Heart Diseases (N=58)	Heart Diseases (N=124)	Heart Diseases (N=66)	Vascular Diseases (N=230)
TOP 3	Respiratory Tract Diseases (N=92)	Metabolic Diseases (N=107)	Central Nervous System Diseases (N=29)	Respiratory Tract Diseases (N=306)	Respiratory Tract Diseases (N=232)	Digestive System Diseases (N=135)	Lung Diseases (N=5)	Respiratory Tract Diseases (N=105)	Respiratory Tract Diseases (N=42)	Respiratory Tract Diseases (N=120)	Digestive System Diseases (N=54)	Respiratory Tract Diseases (N=196)
TOP 4	Syndrome (N=81)	Musculoskeletal Diseases (N=104)	Brain Diseases (N=28)	Communicable Diseases (N=298)	Central Nervous System Diseases (N=194)	Gastro-intestinal Diseases (135)	Respiratory Tract Diseases (N=5)	Lung Diseases (N=92)	Digestive System Diseases (N=41)	Syndrome (N=111)	Gastro-intestinal Diseases (N=54)	Syndrome (N=152)
TOP 5	Communicable Diseases (N=70)	Digestive System Diseases (N=102)	Immune System Diseases (N=22)	Infection (N=298)	Brain Diseases (N=194)	Immune System Diseases (N=132)	Vascular Diseases (N=5)	Digestive System Diseases (N=91)	Gastro-intestinal Diseases (N=41)	Immune System Diseases (N=99)	Central Nervous System Diseases (N=47)	Communicable Diseases (N=151)

N: Number of studies in the respective disease; Note: In some of the countries, the number of studies in the top 5 ranking was the same (e.g. Luxembourg N=5).

## CONCLUSIONS

- Prospective RWE studies still play a minor role in the pharmaceutical research in contrast to clinical trials.
- Large differences in the total number of registered prospective RWE studies was observed across the included European countries. The Nordic countries as well as Belgium and the Netherlands have lower numbers of RWE studies whereas in relation to country size and pharmaceutical market value, the number rises showing the importance of this study type in these regions.
- In addition, the proportion of RWE studies on the overall prospective studies varied between the nations.
- Furthermore, the regulatory requirements strongly depend on the respective country, and the interactions between requirements and pharmaceutical markets should be studied in more detail.
- Vascular and heart diseases as well as respiratory tract diseases are currently of interest within prospective RWE research.

## LIMITATIONS

- Possibly not all studies have been accounted for as not all clinical trials and RWE studies might be registered in this database.
- The diseases reported in the database partly overlap so that a distinct calculation of the top 5 was not possible. Furthermore, only pre-defined diseases instead of aggregated disease categories were analyzed.

## REFERENCES

- Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Vandenbroucke PC, Pocock SJ, et al. (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration. PLoS Med 4(10): e237. <https://doi.org/10.1371/journal.pmed.0040237>
- United Nations, Department of Economic and Social Affairs, Population Division. (2017) World Population Prospects: The 2017 Revision, custom data acquired via website. <https://population.un.org/wpp/>
- efpia, European Federation of Pharmaceutical Industries and Associations. (2017) The Pharmaceutical Industry in Figures, Key Data 2017