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 (Interventional Studies)](expected image)

- 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 treatment 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=23,232), Germany (n=2,260), UK (n=1,763), Italy (n=1,499), Spain (n=1,236), Netherlands (n=791), 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

![Graph showing the number of studies](expected image)

- 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 (19.0 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 (n=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

<table>
<thead>
<tr>
<th>Country</th>
<th>Total Population</th>
<th>Total Number of Prospective Studies</th>
<th>Number of Prospective Studies per 100,000 inhabitants</th>
<th>Pharmaceutical Market Value in €Mio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany</td>
<td>82.3</td>
<td>12,083</td>
<td>5.7</td>
<td>39.0</td>
</tr>
<tr>
<td>UK</td>
<td>66.6</td>
<td>11,141</td>
<td>5.3</td>
<td>27.7</td>
</tr>
<tr>
<td>France</td>
<td>65.2</td>
<td>14,850</td>
<td>5.8</td>
<td>22.4</td>
</tr>
<tr>
<td>Italy</td>
<td>59.3</td>
<td>7,740</td>
<td>7.8</td>
<td>22.4</td>
</tr>
<tr>
<td>Spain</td>
<td>46.4</td>
<td>8,000</td>
<td>7.4</td>
<td>3.8</td>
</tr>
<tr>
<td>Netherlands</td>
<td>17.1</td>
<td>5,788</td>
<td>7.7</td>
<td>4.0</td>
</tr>
<tr>
<td>Belgium</td>
<td>11.5</td>
<td>5,878</td>
<td>7.6</td>
<td>4.0</td>
</tr>
<tr>
<td>Sweden</td>
<td>10.0</td>
<td>3,681</td>
<td>7.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Denmark</td>
<td>5.8</td>
<td>4,892</td>
<td>9.8</td>
<td>3.8</td>
</tr>
<tr>
<td>Norway</td>
<td>5.5</td>
<td>1,758</td>
<td>5.8</td>
<td>2.9</td>
</tr>
<tr>
<td>Luxembourg</td>
<td>5.4</td>
<td>22.38</td>
<td>6.3</td>
<td>1.6</td>
</tr>
</tbody>
</table>

- Regarding the regulatory requirements and guidelines of the European countries, some countries have very detailed regulations whereas others have hardly any legislation at all. In some countries an approval, registration and 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

![Graph showing the top 5 diseases](expected image)

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


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