STUDY PROTOCOL

Outcomes measures in current Danish pharmacoepidemiological research: a protocol for a systematic mapping review [version 1; peer review: awaiting peer review]

Charlotte Thor Petersen1,2, Kristoffer Jarlov Jensen1, Mary Rosenzweig2, Mikkel Zöllner Ankarfeldt1, Gita Kampen2, Janne Petersen1,3

1Phase IV Unit (Phase4CPH), Department of Clinical Pharmacology and Center for Clinical Research and Prevention, Copenhagen University Hospital, Frederiksberg, 2000, Denmark
2DLIMI and Life Science Insight Centre, Copenhagen, 2100, Denmark
3Section of Biostatistics, Department of Public Health, University of Copenhagen, Copenhagen, 1014, Denmark

Abstract
There is a growing interest in complementing the evidence on efficacy and safety of medicinal products gained by randomised clinical trials with real-world data and real-world evidence. Registries provide important sources of real-world data but are typically initiated for administrative purposes. The Danish national registries capture a wide range of information such as health care contacts, social, and economic data; and thereby offer unique possibilities for pharmacoepidemiological research. To gain insight into how registry-based outcome measures from mostly administrative databases are used in real-world evidence studies, the present literature review will investigate the current practice in registry-based studies using Danish health data. A systematic mapping review will be conducted using the literature databases PubMed®/MEDLINE and Scopus®. The search will include Danish registry-based studies aiming at evaluating the effectiveness or safety of medicinal products published from January 1st, 2018 to December 31st, 2019. Data extraction will include the Anatomical Therapeutic Chemical code level 2 of the medicinal product of interest, the outcome measures used, the registry of which the outcome measure has been obtained as well as how the quality of the outcome measure has been considered. The outcome measures extracted will be presented as a categorical overview. These categories will be associated with therapeutic exposure, registry of origin and refereed validation of the outcomes. This systematic mapping review will, as far as we know, be the first of its kind to map outcome measures from Danish national registries used for safety
and efficacy studies.

**Keywords**
Pharmacoepidemiology, Registries, Denmark, Outcome measures, Drugs, Protocol

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**Corresponding author:** Charlotte Thor Petersen (charlotte.thor.petersen.01@regionh.dk)

**Author roles:**
- **Thor Petersen C:** Conceptualization, Methodology, Writing – Original Draft Preparation, Writing – Review & Editing;
- **Jensen KJ:** Conceptualization, Methodology, Supervision, Writing – Review & Editing;
- **Rosenzweig M:** Conceptualization, Methodology, Supervision, Writing – Review & Editing;
- **Ankarfeldt MZ:** Writing – Review & Editing;
- **Kampen G:** Writing – Review & Editing;
- **Petersen J:** Conceptualization, Methodology, Supervision, Writing – Review & Editing

**Competing interests:** No competing interests were disclosed.

**Grant information:** The author(s) declared that no grants were involved in supporting this work.

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**How to cite this article:** Thor Petersen C, Jensen KJ, Rosenzweig M et al. Outcomes measures in current Danish pharmacoepidemiological research: a protocol for a systematic mapping review (version 1; peer review: awaiting peer review) F1000Research 2021, 10:368 https://doi.org/10.12688/f1000research.52727.1

**First published:** 10 May 2021, 10:368 https://doi.org/10.12688/f1000research.52727.1
**Introduction**

Randomised clinical trials (RCTs) are the “gold standard” to demonstrate the efficacy of a medicinal product – “if the product can work” – under controlled conditions. Randomisation reduces the bias due to baseline confounding and is therefore a major asset of RCTs. However, RCTs are often conducted on a more homogenous patient population in relation to age, disease severity, comorbidities, and comedication compared to those patients seen in clinical practice as well as in a more specialised “ideal” setting. Furthermore, RCTs are often limited in number of participants and duration, which can prevent the observation of rare events or assessment of long-term effects. These factors can limit the generalisability of RCTs. Real-world evidence (RWE) studies can offer important complementary information to the evidence established in RCTs. RWE studies provide a mean to gain information regarding the effectiveness of a medicinal product – “if the product actually does work” - in routine clinical practice (real-world setting).

The interest and focus on RWE studies on effectiveness and safety of medicinal products has been increasing. The European Medicines Agency (EMA) and the U.S. Food and Drug Administration (FDA) have long had the authorisation to require the pharmaceutical industry to perform both post-authorisation safety studies and post-authorisation efficacy studies. However, within the last couple of years, both EMA and FDA have begun the process of developing new regulatory frameworks and guidelines for the use of real-world data (RWD) and RWE to support, for example, determination of product effectiveness and safety, or approval of new indications for the medicinal product. One important source of RWD is registries, which can provide information about diseases, patients characteristics, utilisation and outcomes of treatments.

Denmark has a long history of maintaining nationwide registries capturing a wide variety of longitudinal population-based data. In Denmark, information regarding redeemed prescriptions and in-hospital medication use is registered using the Anatomical Therapeutic Chemical (ATC) classification system, which can be interlinked on individual level through the unique personal identifier, the Central Personal Register number, to data from patient registries, prescription registries, registries containing laboratory data, or contacts with general practitioners and other medical specialists, several registries on sociodemographic and employment status, 84 clinical quality databases as well as several research databases. An overview of the Danish health data and more than 150 registries/databases is available from the Copenhagen Healhtech Cluster webpage. These data offer unique possibilities for Danish pharmacoepidemiological research to evaluate the effectiveness and safety of medicinal products in clinical practice. The national registries in Denmark are mainly developed for purposes of financial accounting and quality control. Therefore, it is important to be aware of the potential limitations of these registries such as uncertain validity of data or missing important outcomes when used for RWE studies. It can be challenging to identify validated and reliable outcome measures for RWE studies. For example, the limitations of the data available in the registries may necessitate the choice of outcomes which are not clinically most relevant. In order to help identifying potential, but hitherto unexplored registry-based outcome measures, that can better target the clinical scope of RWE studies evaluating the effectiveness and safety of medicinal products, an investigation of the currently used outcomes measures is required.

Thus, the objectives of this systematic mapping review are: (1) to give an overview of the types of outcome measures currently used in Danish registry-based studies evaluating the effectiveness or safety of medicinal products, and link these to the therapeutic exposure (ATC level 2) and to the registries of origin; and (2) to investigate how the studies address the quality (reliability, validity and responsiveness) of the outcome measures used.

**Protocol**

The study is conducted as a systematic mapping review. Systematic mapping reviews provide overviews of research characteristics within a topic area by structuring and categorising the existing literature. The systematic mapping review focuses on the research practices related to the findings, e.g. the methodology or publication characteristics of the included studies.

The screening is expected to begin in December 2020. This will be followed by the data extraction which is expected to begin in March 2021.

**Eligibility criteria**

**Study characteristics**

This systematic mapping review will include registry-based studies reported in English and published in the period January 1st, 2018 to December 31st, 2019 describing original research on the relationship between exposure of a medicinal product and an effectiveness/safety outcome, where data on outcomes are obtained from Danish registries or databases.

The terms “exposure of a medicinal product” must comply with the EMA definition of a medicinal product available from the EMA webpage glossary: “A substance or combination of substances that is intended to treat, prevent or diagnose a disease, or to restore, correct or modify physiological functions by exerting a pharmacological, immunological or metabolic action”.

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Information resources and search strategy

The literature search strategy will be developed and completed first in the electronic database PubMed®/MEDLINE using free text words and Medical Subject Headings (MeSH) related to Danish registry-based research on effectiveness or safety of medicinal products. The development of the search strategy will be achieved by testing different combinations of search terms. For each combination, the resulting number of records (N) will be noted and the relevancy of the search will be determined by screening the first 10-20 article headlines and summaries when the PubMed®/MEDLINE search is sorted by: Best Match. Each identified search term will be continuously evaluated for its relevance in the final search string. In addition, the search string may be further specified using the [Title/Abstract] search field tag. The final search string developed in PubMed®/MEDLINE is stated below.

In order to identify and categorise the currently used outcome measures in Danish registry-based studies, we aim at including approximately 250 articles for data extraction. We believe that the relatively short two-year publication period limiting the inclusion will be representative of the current practice but at the same time reduces the number of Covid-19 related studies included as despite of their relevance, these will potentially skew the picture of outcome measures used to evaluate the effectiveness and safety of medicinal products.

Following the completion of the search strategy in PubMed®/MEDLINE, the same strategy will be applied in the electronic database Scopus® to ensure a more comprehensive literature search. The final search string applied to Scopus® is available below. The results of the literature searches in PubMed®/MEDLINE and Scopus® serve as input for the screening process.

**PubMed®/MEDLINE (performed 18th November 2020; 783 records)**

"registries"[MeSH Terms] OR "registries"[TIAB] OR "registry"[TIAB] OR "register"[TIAB] OR "registers"[TIAB]) AND ("danish"[TIAB] OR "denmark"[MeSH Terms] OR "denmark"[TIAB]) AND ("therapeutics"[MeSH Terms] OR "drug therapy"[MeSH Subheading] OR "therapeutic use"[MeSH Subheading] OR "drug therapy"[MeSH Terms] OR "therapeutic use"[MESH Subheading]) AND ("pharmaceutical preparations"[MeSH Terms] OR "medication"[TIAB] OR "medications"[TIAB] OR "drug"[TIAB] OR "Pharmacoepidemiology"[MeSH Terms] OR "Pharmacoepidemiology"[TIAB]) Filters: Humans, English, from 2018/1/1-2019/12/31

**Scopus® (performed 6th December 2020; 463 records)**

TITLE-ABS-KEY ("registries" OR "registry" OR "register" OR "registers") AND ("danish" OR "denmark") AND ("therapeutics" OR "drug therapy" OR "therapeutic use" OR "pharmaceutical preparations" OR "medication" OR "medications" OR "drug") AND PUBYEAR > 2017 AND PUBYEAR < 2020 AND (LIMIT-TO (LANGUAGE, "English"))

Study records

Validation of selection process

Prior to the screening process, three researchers will conduct a validation of the eligibility criteria to ensure consensus. Each researcher will independently review the title and abstract of 20-40 randomly selected records from the literature search, and categorise them into “relevant”, “unsure”, or “irrelevant”. If agreement is reached, the screening process will proceed. In case of disagreement, the three researchers will decide together and potentially correct or specify the eligibility criteria.

Selection process

The study records obtained from the literature searches in PubMed®/MEDLINE and Scopus® will be screened by one of the three researchers based on title and abstract using Rayyan® review software, and the records will be categorised as stated above. Records categorised as “unsure” will be screened independently by the two other researchers. The three researchers will discuss the results and decide together how to categorise these records.

Validation of data extraction

Prior to data extraction, the process and the item list (Table 1) will be checked and validated to ensure uniform interpretation. Data extraction of minimum 30 randomly selected eligible studies will be conducted independently by at least three researchers. If agreement is reached in ≥80% of the cases, the data extraction process will proceed. If disagreement occurs in >20% of the cases, a larger number of articles will be included in the validation process.
Table 1. Data items used to score articles.

| Data item | Description | Scoring |
|-----------|-------------|---------|
| **Publication characteristics and eligibility assessment** | | |
| Author(s) | The author(s) of the article. | Text string |
| Title | The title of the article. | Text string |
| Journal | The journal in which the article was published. | Text string |
| Publication year | The year in which the article was published. If the article has been published in both print and electronic, the print year of publication will be stated. | Number |
| Language | Is the language of publication English? | Yes No |
| Exposure | Does the exposure of interest comply with the EMA definition of a medicinal product? | Yes No |
| Registry-based | Is the exposure-related outcome(s) obtained from a Danish registry/database? | Yes No |
| Eligibility | The article will be included for further data extraction if "Language", "Exposure", and "Registry-based" are all scored "Yes". Otherwise, the article will be excluded, and no further data extraction will be performed. | Include Exclude |
| **Study characteristics** | | |
| Study design | The type of study design, e.g. cohort study, case-control study, nested case-control study, case-cohort study, cross-sectional study, etc. Descriptive adjectives such as a “matched” cohort study will also be stated. | Text string |
| Patient enrolment_start | The year in which patient enrolment begins. | Number |
| Patient enrolment_end | The year in which patient enrolment ends. | Number |
| Request | Whether the study was imposed by EMA, FDA, or other? | EMA FDA Other Not specified |
| **Data of interest** | | |
| Medicinal product_ATC1 | The ATC 1st level of the medicinal product(s) of interest. If the ATC code is not explicitly stated, it will be found based on the generic product name using the searchable version of WHOCC - ATC/DDD Index. In the case, where neither the ATC code nor the generic product name is available, the medicinal product exposure will be categorised as "Other". | A: Alimentary tract and metabolism B: Blood and blood forming organs C: Cardiovascular system D: Dermatologicals G: Genito urinary system and sex hormones H: Systemic hormonal preparations, excluding sex hormones and insulin J: Anti-infective for systemic use L: Antineoplastic and immunomodulating agents M: Musculoskeletal system N: Nervous system P: Antiparasitic products, insecticides and repellents R: Respiratory system S: Sensory organs V: Various. Other |
If disagreement continues, the entire assessment for eligibility and data extraction will be conducted by more than one researcher. During this validation process, the item list will potentially be corrected or specified.

**Data extraction**

Articles assessed as “relevant” will be full-text reviewed by one researcher for eligibility based on criteria stated under the section “Eligibility criteria”. The excluded articles will be assigned a reason for exclusion. In case of doubt, one or more

### Table 1. Continued

| Data item                | Description                                                                 | Scoring                   |
|--------------------------|-----------------------------------------------------------------------------|---------------------------|
| Medicinal product_ATC2   | The ATC 2nd level of the medicinal product(s) of interest. If the ATC code is not explicitly stated, it will be found based on the generic product name using the searchable version of WHOCC - ATC/DDD Index. | Text string               |
| Outcome measure_specific | The specific Danish registry-based exposure-related outcome measure assessed in the study. | Text string               |
| Outcome measure_subgroup | The Danish registry-based outcome measure assessed in the study are categorised into the subgroup given in the scoring column. If no subgroup is applicable, the outcome measure will be scored as “Other”. See Table 2 for the definition of each subgroup. | Apgar Score<br>All-cause death<br>All-cause death offspring<br>Cause-specific death<br>Cause-specific death offspring<br>Cost<br>Diagnosis<br>Diagnosis offspring<br>Diagnosis/prescription combination<br>Diagnostic measures<br>Drug discontinuation/switch<br>Healthcare utilisation<br>Hospitalisation<br>Physical ability test<br>Preterm birth<br>Prescription<br>Severity scale (Disease)<br>Small for Gestational age (SGA)<br>Surgery and procedures<br>Quality of Life (QoL)<br>Work ability/Productivity/Connection to labour market<br>Other |
| Outcome measure_registry | The specific registry(ies) from which the outcome measure has been obtained. If more than one registry has been used, an additional column will be added in the extraction sheet. | Text string               |
| Outcome measure_quality  | If applicable, the sentence(s) in which the article states, comments or consider the quality of the specific outcome measure used or the registry from which it has been obtained will be extracted. Otherwise, the item will be scored as “Not considered”. The following terms will be sought systematically: reliability, reproducibility, validity, specificity, completeness, sensitivity, positive predictive value (PPV), negative predictive value (NPV), responsiveness, and responsive. The terms must be related to the outcome measure or registry. | Text string               |
| Outcome measure_quality reference | If applicable, the reference used to support the quality of the specific outcome measure or the registry from which the outcome measure has been obtained. Otherwise scored as “NA”. | Text string               |

If disagreement continues, the entire assessment for eligibility and data extraction will be conducted by more than one researcher. During this validation process, the item list will potentially be corrected or specified.
researchers will be consulted. The result will be reported as a modified PRISMA 2009 Flow Diagram.\textsuperscript{27} Data from the studies identified as eligible will be extracted and scored according to the item list (Table 1) and the outcome measures will be categorised into the subgroups defined in Table 2. Data related to sensitivity analyses will be ignored. In the prepared data extraction sheet, the data extraction is controlled by the ATC level 2 of the exposure of interest and the outcome measure. Thus, if more than one medicinal product is investigated which differ in ATC level 2, or if more than one outcome measure is presented in a study, a new row will be established for each medicinal product or outcome measure with the same information stated in the previously extracted items (Table 1). The data items in Table 1 were identified based on (1) one researcher performing a data extraction test of relevant articles identified in the early process of search strategy development,\textsuperscript{28–34} (2) a review protocol on incident- and prevalent-user designs in observational comparative effectiveness and safety studies,\textsuperscript{35} (3) the hypothetical categorical overview of outcome measures presented in Table 3, and (4) from general discussion between the co-authors of which items could be relevant for this study and how to score them.

Table 2. Definitions of outcome measure subgroups.

| Outcome measure subgroup:                           | Outcome measures included (not exclusively):                                         |
|-----------------------------------------------------|--------------------------------------------------------------------------------------|
| Apgar Score                                         | 1-min, 5-min, or 10-min Apgar Score                                                 |
| All-cause death                                     | All-cause death/mortality, survival                                                 |
| All-cause death offspring                           | All-cause death/mortality in offspring, survival in offspring, stillbirth, foetal death |
| Cause-specific death                                | Death related to a specific cause e.g. death by heart failure or by suicide.         |
| Cause-specific death offspring                      | Death related to a specific cause in offspring                                       |
| Cost                                                | May include cost associated with inpatient or outpatient services, services obtained in the primary sector, medication cost, or non-health-related costs. |
| Diagnosis                                           | Outcome measures defined by (time-to-) diagnosis.                                  |
| Diagnosis offspring                                 | Outcome measures defined by (time-to-) diagnosis in offspring/children.             |
| Diagnosis/Prescription combination                  | Combined outcome measure of diagnosis and prescription of a specific medication other than the medicinal product of interest. |
| Diagnostic measures                                 | Measurable indicators for the severity or presence of a disease or condition, e.g. a specific biomarker. |
| Drug discontinuation/drug switch                    | Outcome measures defined as (time-to-) drug survival, drug discontinuation or drug switch |
| Healthcare utilisation                              | May include hospital admissions, hospital days, outpatient visits, general medication use or other health-related services. |
| Hospitalisation                                     | Hospitalisation not defined by diagnosis.                                           |
| Physical ability test                               | Tests used to evaluate the patient’s physical or functional ability                  |
| Preterm birth                                       | Preterm birth                                                                       |
| Prescription                                        | Prescription of specific medication other than the medicinal product of interest      |
| Severity scale (Disease)                            | Instruments used to determine the severity of a disease/disease activity as well as evaluate treatment response e.g. Psoriasis Area and Severity Index (PASI). |
| Small for Gestational Age (SGA)                     | Small for gestational age (SGA)                                                     |
| Surgery and procedures                              | Outcome measures defined as surgery or procedures e.g. with use of procedure codes. |
| Quality of Life (QoL)                               | (Health related) Quality of Life instruments, e.g. Dermatology Life Quality Index (DLQI) or EuroQol 5D (EQ-5D) |
| Work ability/Productivity/Connection to labour market| Can include both measures of objective and perceived work ability or productivity, lost workdays due to health or as consequence of sick-leave, or other. |
| Other                                               | Outcome measures which do not fit into one of the above stated subgroups.             |
Data synthesis
In the final report, the results will be presented as a categorical overview in which the outcome measures will be assigned into different outcome categories (with potential subcategories) according to the type of measure (e.g. clinical, work-related, economic and utilisation, humanistic). The hypothetical categorical overview presented in Table 3, a result of preliminary literature research and conceptualisation, has helped shaping the project idea and served as a starting point for conducting the systematic mapping review. It is important to note that the stated outcome measures cannot necessarily be obtained from Danish registries. Furthermore, the outcome measure categories/subcategories are not completely mutual exclusive.

In addition, the resulting outcome measures subgroups will be presented as absolute numbers and percentages of the total number of studies analysed and will be linked to (1) the therapeutic exposure on ATC level 2, and (2) to the specific registry from which outcome measure has been obtained. In addition, a table summarising the information collected for each study included in the analysis will be made available. How the studies have addressed the quality of the outcome measure used will be used in a narrative interpretation and discussion of the results.

Ethical considerations
This study is exempt from ethical approval as the review is conducted on already published studies.

Dissemination plan
Amendments to the systematic mapping review will be disseminated along with the findings in an international peer-review journal.

Discussion
A literature review mapping and categorising outcome measures used in Danish registry-based studies across different therapeutic areas, has to our knowledge never been conducted. However, some limitations associated with the study design are important to notice. The review will only include studies published in English which may introduce language bias, though we expect only a negligible number of publications in Danish, as Danish is a small language and therefore most scientific communication is made in English. The studies included will be limited by a two-year publishing period; January 1st, 2018 to December 31st, 2019. Thus, the results of the systematic mapping review are expected to be representable of the current practice within Danish registry-based studies but will be unable to depict the historical development within the field.

Data availability
Underlying data
No data are associated with this article.

Table 3. Hypothetical categorical overview of outcome measures.

| Outcome measures                                | Clinical | Work-related | Economic and utilisation | Humanistic or Patient-reported outcomes (PROs) |
|-------------------------------------------------|----------|--------------|--------------------------|-----------------------------------------------|
| Mortality/survival                               | Disease (process) and therapy measures | Diagnostic measures | Functional measures |                                   |
| Cause-related mortality, All-cause mortality     | Diagnosis/disease occurrence, %-healed, Hospitalisation, Disease recurrence, Response rate, Adverse events, Prescriptions | Tumour biomarkers, Serum cholesterol, Antibody concentration, Vital signs – respiratory rate, blood pressure, X-ray, CT scans | Physical ability tests, Completed repetitions, Walk-test | Work ability/productivity, Lost workdays due to health |
| Health care cost                                | Healthcare utilisation (e.g. hospital admission, hospital days) | Medication cost | Medication use | HRQoL instruments Symptom status/ reports Treatment preferences Symptom-free days, Patient function (physical, mental, social) |

HRQoL = Health-Related Quality of Life.
Reporting guidelines

The EQUATOR Network contain no reporting guidelines for systematic mapping reviews. Thus, the importance of disseminating the present study protocol is to achieve optimal transparency and consistency in the review method used.

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