Trial Nation
Clinical Trials Denmark

Phase IV Trial Union

A network of Phase IV units in Denmark

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Phase IV Trial Union

Denmark is an ideal country for conducting different types of phase IV activities. Trial Nation Phase IV Trial Union is a network of Danish phase IV units specialized in research and execution of studies on marketed drugs with a real-world evidence (RWE) perspective.

The Phase IV Trial Union covers all regions of Denmark and, therefore, offers a single point of contact to a dedicated, national network of units with a strong focus on collecting data that meets the requirements from authorities and health economic bodies to pharmacoepidemiologic registry studies and clinical research in a variety of therapeutic areas and with unique access to 250+ general practitioners (GP).

The phase IV units are staffed with experienced epidemiologists, biostatisticians data experts and specialists in pharmacology working in close collaboration with clinical, legal and admin specialists. The teams have extensive experience in designing studies and analyzing data linked from multiple data sources. Trial Nation offers one point of contact to the Phase IV Trial Union for research collaboration on phase IV projects.

PHASE IV TRIAL UNION SERVICES

Over the past decades, the phase IV units in Denmark have built up considerable expertise in registry studies and clinical trials by conducting investigator-initiated research, research in collaboration with universities and authorities (e.g., FDA, EMA) as well as with companies in company-sponsored studies, often based on a post-authorization safety study (PASS) commitment. The types of projects range from small-scale specialized assessments over large registry studies based on several of the unique Danish health registries to prospective large-scale pragmatic trials recruiting patients from a large number of general practice clinics and complying with Good Clinical Practice standards.

The units have extensive experience in planning and designing studies, programming infrastructure, statistical modeling, and on analyzing data linked from diverse data sources.

Experience with clinical trials, research interest and specific research competencies vary across the units and the following types of activities are covered.

- registry studies,
- post-authorisation safety studies (PASS) and post-authorization effectiveness (PAES) studies,
- comparative effectiveness research (CER),
- real-world evidence on drug utilization, safety, effectiveness,
- methodical development on drug profiles,
- healthcare utilization and health economics,
- pragmatic clinical trials,
- variability in drug effects,
- augmented clinical trials, e.g., clinical trials augmented with health data/registry data, external or historic control arms, analyses of representativeness, streamlined trials, follow-up in

registries, remote or decentralized trials.

- clinical trials in general practice/primary care settings*

*The studies in primary care settings that are primarily covered, are limited to the following: Studies of marketed drugs primarily addressing safety questions including PASS.

The Danish Phase IV Units

Unit	Contact
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Contact

For a coordinated request to all units, please contact Lene Hartmann: lhar@regionsjaelland.dk

Contact information on key contacts at the individual departments are available in the table above

Case Studies

SCOT – A pragmatic, streamlined trial in general practice

Phase IV trial with 2,209 patients randomized in Denmark, Standard care vs Celecoxib Outcomes Trial. Randomized trial of celecoxib vs traditional NSAID regarding the development of thrombosis. 216 GPs involved. (Read more here: Randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib: the Standard care vs. Celecoxib Outcome Trial (SCOT) - PubMed (nih.gov))

Conducted by the SDU Clinical Trial Unit. Ref. Professor, consultant MD Jesper Hallas.

Pharmacoepidemiologial studies of tamoxifen based on Danish registries and biobanks

Over the past 15 years, breast tumors have been collected from hospitals all over Denmark. These were linked with data from national registers and a variety of analyses were conducted, such as genetic factors for pharmacokinetics, biomarkers, use of prescription medication, comorbidities, relation to recurrence of cancer, early discontinuation of tamoxifen treatment, and long-term survival of the patients. The studies have included multinational collaboration and funding from, e.g., the National Cancer Institute, USA.

> 31 publications. Read more and see an example here: Metabolic Pathway Analysis and Effectiveness of Tamoxifen in Danish Breast Cancer Patients and CYP2D6 inhibition and breast cancer recurrence in a population-based study in Denmark.

Conducted by DCE. Ref. Professor Henrik Toft Sørensen.

Safety of duloxetine during pregnancy

A cohort study on pregnancies in Denmark and Sweden between 2004-2016, >2 million cases. Safety data was provided to EMA. Read more here: Exposure to duloxetine during pregnancy and risk of congenital malformations and stillbirth: A nationwide cohort study in Denmark and Sweden - PMC (nih.gov)

Conducted by Phase4CPH. Ref. Associate Prof. Janne Petersen, University of Copenhagen.

Insights on medication adherence: The role of patient-reported data

A patient-focused approach is advocated to address the risk of non-adherence to medication and subsequent adverse clinical outcomes. By linking surveys with patient-reported data with national registries, detailed insights on the role of various patient-reported factors were obtained, including the impact of information on pharmacological treatment perceived by the patients, quality of life and symptoms of depression. Read more in this example: Patient-reported outcomes and medication adherence in patients with heart failure.

Conducted by Danish Center for Health Services Research. Ref. Professor Søren Paaske Johnsen.

Examples of how health data could possibly be used in augmented clinical trials

FAST trial - study follow up via health registers

In the FAST trial (https://pubmed.ncbi.nlm.nih.gov/33181081/), a new anti-gout drug, feboxustat, was compared to allopurinol with respect to cardiovascular safety. Patients who were already treated with allopurinol were randomized to either continue allopurinol or to switch to febuxostat. Patients had only one study-related visit, the one in which informed consent was taken and randomization carried out. Patients were followed for up to six years with respect to major cardiovascular outcomes. Follow-up was carried out by regular health register queries, wherein hospital contacts that could represent cardiovascular were ascertained. If a potential outcome of interest occurred, medical records were retrieved, and outcomes were adjudicated by an expert panel. By refraining from having routine study-related visits, the costs of the trial were dramatically reduced without compromising the validity of the trial.

SORT OUT X trial - comparison of 3-year outcomes via health registries

In the SORT OUT X trial (Dual-therapy CD34 antibody-covered sirolimus-eluting COMBO stents versus sirolimus-eluting Orsiro stents in patients treated with percutaneous coronary intervention: the three-year outcomes of the SORT OUT X randomised clinical trial | EuroIntervention (pcronline.com)) two types of stents were compared in a prospective multicentre randomized clinical trial with a registry-based follow-up. The 3-year outcomes of the DTS and the sirolimus-eluting Orsiro stent (SES) in all-comer patients treated with percutaneous coronary intervention were compared via health registers. The primary endpoint, TLF, was a composite of cardiac death, myocardial infarction or target lesion revascularization (TLR). At 3 years, the SES stent was found superior to the DTS, mainly because the DTS was associated with an increased risk of TLF within the first year but not from 1 to 3 years. The possibility to use Danish health registers could reduce costs of the trial significantly.

The TASTE trial - another example of a study design including health registry data

In the TASTE trial (https://pubmed.ncbi.nlm.nih.gov/23991656/, ClinicalTrials.gov number,

NCT01093404.) clinical effect of routine intracoronary thrombus aspiration before primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI) was investigated. A total of 7244 patients with STEMI undergoing PCI were randomly assigned to PCI with or without manual thrombus aspiration. The primary endpoint was all-cause mortality at 30 days which was ascertained through national registries. The trial concluded that routine thrombus aspiration did not reduce 30-day mortality among patients with STEMI. It is worth noting that due to the use of registers, none of the 7244 patients were lost to follow up, and the total expense of the entire trial was in the order of $1 million.

Why Phase IV Studies?

With phase IV (post-approval) studies, it is possible to learn about drugs post-approval in a real-world setting which is not always possible using the data collected from traditional randomized clinical trials (RCT). Some of the main reasons to perform RWE studies are:

- Adverse effects can be confused with spontaneous adverse events, thus
    - overlooking adverse effects,
    - perceiving adverse events as adverse effects.
- Adverse effects cannot always be studied by RCT. This could be because there is too short follow-up period, the safety outcome is very rare and a very large sample size would be necessary, or of ethical reasons.. For the study of some adverse drug reactions, e.g., drug induced congenital malformations, RCTs would clearly be unethical.
- There are reporting systems for adverse events, but, not all adverse drug effects are visible to individual clinicians.
- Drugs are not used by those they were intended for, in ways that were intended.
- A balanced view on benefit, risks and price is essential to achieve rational use of medicines.

WHY CHOOSE DANISH PHASE IV TRIAL UNION FOR PHASE IV STUDIES?

- State-of-the-art researchers and research methodologies to conduct continuous surveillance or specific specialized studies
    - expertise in collaboration with companies
    - programming infrastructure to increase efficiency
    - epidemiological statistical modelling
    - data infrastructures on larger disease areas
    - network of clinicians and researchers
- Access to high-quality registries with complete population coverage (including the CPR registry that makes it possible to collect information about the same person in several independent registries) and expertise in linking records from multiple and diverse data sources.
- The Danish phase IV units collaborate across hospitals, universities and regions and together have access to a large population across the whole of Denmark for the conduct of clinical trials, including access to a nationwide network of general practitioner clinics.
- Denmark is a country with current high political attention on the whole life science area and access to the unique Danish health registries.
- Close collaboration with other Nordic countries.

Trial Nation

Get in touch

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