

Applying for linked data from the Lifelines Cohort Study and IADB.nl database



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Introduction

The Pharmlines Initiative, started in 2017, is a collaboration between three data sources (Lifelines, IADB.nl, and CBS Microdata Services) with the goal to facilitate scientific research in the combined fields of a) healthy ageing, b) pharmaco-epidemiology/therapeutics/ economics and c) Dutch population statistics.

To reach this goal, the three data sources have developed a procedure in which any qualified researcher with a valid project proposal may request access to the required combined datasets.

In this document, some background information on the Pharmlines Initiative is provided and the procedure to gain access is described.

Lifelines Cohort Study

Lifelines is a longitudinal population cohort study collecting data and samples from over 167,000 participants over a period of thirty years. Lifelines participants are residents of the northern parts of the Netherlands and cover three generations: 15,000 children (0-18), 140,000 adults and 12,000 elderly (65+). Participants periodically undergo physical measurements, fill out extensive questionnaires, and donate blood and urine samples. A comprehensive overview of the collected data and samples can be found in the Lifelines [wiki](#) and [data catalogue](#).

Lifelines has the aim to make the collected data [data and samples](#) available for researchers and policy-makers interested in promoting healthy ageing. Qualified researchers and policy-makers (worldwide) with a valid project proposal can [apply](#) for the use of Lifelines data and/or samples for scientific research (see Appendix A for criteria). Thus far, more than 500 research projects have been approved and more than 400 scientific papers using Lifelines data have been published.

IADB.nl database

The University of Groningen IADB.nl pharmacy prescription database is a growing database that contains prescription data from 1994 till 2019 from approximately 100 community pharmacies, and covers an estimated population of 930,000 patients (situation January 2021). Registration in the database is irrespective of health care insurance. Age, gender and prescription rates among the database population have been found to be representative of the Netherlands as a whole, and the database has been widely used for research.

Each person is individually tracked throughout the database period and prescription records contain information on the date of dispensing, the quantity dispensed, the dose regimen, the number of days the prescription is valid, the prescribing physician (GP or specialist) and the Anatomical Therapeutic Chemical code (ATC code). Each patient has a unique anonymous identifier; date of birth and gender are known. Due to the high

patient-pharmacy commitment in the Netherlands, the medication records for each patient are virtually complete, except for over the counter (OTC) drugs and medication dispensed during hospitalization.

CBS Microdata

The Centraal Bureau voor de Statistiek (CBS, internationally known as Statistics Netherlands), founded in 1899, is a Dutch governmental institution that gathers statistical information about Dutch citizens. The bureau is located in The Hague and Heerlen. Since 3 January 2004, Statistics Netherlands has been a self-standing organisation, or 'quango'. Its independent status in law guarantees the reliable collection and dissemination of information supporting public debate, policy development and decision-making.

CBS Microdata are linkable data at the level of individuals, companies and addresses which can be made available to Dutch universities, scientific organisations, planning agencies and statistical authorities within the EU under strict conditions for statistical research. The range of subject areas includes socio-economic data, health and welfare data and causes of death of Dutch citizens.

The Pharmlines Initiative

Researchers interested in the combined data from all three data sources may apply for access via the Pharmlines Initiative procedures (note that the use of all three sources is mandatory and must be properly substantiated).

In order to minimize the transportation of identifying personal data and to organize the process of linking and giving access to data in a legally and ethically acceptable manner, personal data collected and controlled by Lifelines, IADB.nl and CBS are linked and released within the CBS infrastructure. Importantly, CBS has unique know-how and experience in storing, pseudonimizing and encrypting personal data for scientific analysis and output.

Lifelines developed a linkage file with unique CBS-pseudonyms for all its participants (reference date 28-2-2017; n=167,487). For any approved project, the required data from Lifelines participants can be safely and securely be uploaded to the CBS infrastructure using the CBS pseudonyms, and processed for linkage by CBS data managers.

IADB.nl uploaded a dataset on medication use from the IADB.nl database to CBS. As of January 2021, data of 930,000 persons with information on medication use from 1994 till 2021 are available withing the CBS infrastructure.

The requested Lifelines and IADB.nl data will be made available, together with the requested CBS Microdata (e.g. mortality statistics), via the Remote Access secure virtual work environment of CBS. More information about this work environment can be found at the [CBS website](#). The usual formalities, procedures and costs of Statistics Netherlands apply for the use of this working environment.

The procedures on data request and data access are described below.

Procedure on data request

In general, all researchers are advised to prepare their project using the available online resources such as the Lifelines wiki, Lifelines data catalogue, IADB.nl website, and CBS Microdata catalogue. Any remaining questions can be e-mailed to the Lifelines research office (research@lifelines.nl) and/or the IADB (info@iadb.nl).

Once prepared, the following steps must be taken in order to ensure a rapid procedure.

1. Applying for Lifelines data

Researchers must first apply for Lifelines data by submitting a research proposal to Lifelines (following the Lifelines [application process](#)) or, alternatively, an amendment to an approved and active research proposal, in which the scientific purpose of using combined Lifelines, IADB, and CBS data is explained. The proposal must be submitted together with a variable selection via the online [Lifelines data catalogue](#). An amendment without additional variable selection may be e-mailed instead to research@lifelines.nl. If

you have any questions regarding the application process, please contact the Research Office via e-mail.

2. Applying for IADB.nl data

Researchers must also submit a preliminary [IADB.nl protocol](#) to info@iadb.nl in parallel with the Lifelines application. This protocol is used to register the research and to make sure the right data formats are prepared and the design and analyses are agreed. It is strongly advised to contact info@iadb.nl before starting an application to discuss the value of the data for the research question. A preliminary version of the protocol is sufficient at this stage, a completed protocol must be submitted prior to the start of data analysis.

Both Lifelines and IADB will review the research proposal or amendment (for review criteria see appendix A), and IADB will review the preliminary protocol. When all is approved, Lifelines will confirm the approval of both parties via email.

3. Applying for CBS data

Once Lifelines and IADB have approved the proposal/amendment, a completed [application form of CBS Microdata services](#) must be submitted to microdata@cbs.nl. Please mention 'the Pharmlines' initiative in the title, and state that you have received the required approval.

Once the project is approved by CBS, it can be carried out definitively. CBS Microdata Services will confirm the approval and assign the project a Project Code.

Note (1) that you must use microdata from Statistics Netherlands in your project (i.e. it is not possible to link only Lifelines and IADB data).

Note (2) that you may agree with CBS on a starting date in the future. Not specifying a starting date will result in an immediate start of the project at CBS. If you still need considerable preparation time, please be aware of this.

4. CBS Contract, offer and RMAA

The following contracts must be drawn up and signed, in order:

- CBS Project Agreement. Once this is signed, please send a copy to Lifelines, since this is a required appendix to the three-party RMAA (see below).
- CBS will also send an indication of costs that includes costs for: project start-up, pseudonimization of participants, temporary use of the remote access environment of CBS and the use of their microdata files. More information about the costs charged by CBS can be found in the [Service Catalogue](#).
- Lifelines will send a Research Material Access Agreement (RMAA). The signed project agreement of CBS will be included in the appendix. The RMAA must be

signed by the researchers (legally represented by the head of their academic department or institute), IADB.nl (legally represented by the University of Groningen) and Lifelines. Please make sure that in all documents, the roles of representatives of institutes, recipient and PI are consistent and clearly defined.

- Together with the RMAA, Lifelines will send an offer to the researchers that includes: 1) a fee for the use of the Lifelines data (ask research@lifelines.nl for the project-specific fee), and 2) €1,000 for the use of the data on IADB.nl medication use.

After the contracts have been signed, the researchers need to finalize the IADB.nl protocol (see [IADB.nl](#)) and submit it as a final version to make sure the right data formats are prepared and the design and analyses are agreed upon.

Procedure on data access

For each approved project, a Lifelines dataset will need to be uploaded to CBS. The required data may be already present in an active workspace (in case of an amendment). If not, a workspace must be opened for a period of at least 6 months to be able to access the data selection submitted via the Lifelines data catalogue.

Researchers must process the dataset in the workspace for the following reasons:

- Get fully acquainted with the Lifelines data and discuss any issues/questions/missing variables with Lifelines data management (as this is more difficult after linkage);
- Minimize the amount of variables to be uploaded (strict selection of variables such as SNPs, use of sum scores rather than raw data);
- Minimize the number of data files (preferably to 1) via merging;
- Log all minimalization and merging actions, for example in syntaxes, so that Lifelines data management can trace them back.

After the linkage file has been checked by a Lifelines data manager, Lifelines will upload the file to CBS. CBS will then pseudonymize the participant ID's in the uploaded data file in such a way that they can be linked to pseudonyms in the IADB.nl database and to pseudonyms in the CBS Microdata files. This step takes approximately 2 weeks. After CBS has informed IADB.nl that the Lifelines data is ready for use, IADB will add these data to the project database (SQL server) within the CBS virtual work environment. Since the combined Lifelines and IADB.nl data is only accessible via the SQL server, all analyses must be performed on this SQL server.

Support

During the execution of the research project, researchers can receive the following support:

- IADB.nl database: the staff of the IADB.nl will help with the protocol, registration of the study, training and testing of using the data. Staff can be reached via info@IADB.nl
- Lifelines Biobank and Cohort Study: questions regarding the Lifelines data can be sent to the data managers of Lifelines (data@lifelines.nl)
- Microdata service Statistics Netherlands: questions regarding the use of the remote access environment of Statistics Netherlands can be sent to microdata@cbs.nl.

Research and Data Management Plan (RDMP)

All data analyses and results that are exported from the CBS environment to the researcher must be returned to IADB (info@IADB.nl) and Lifelines (data@lifelines.nl), where they will be stored according to IADB (RuG RDMP) and Lifelines standards.

Evaluation of the research project

All research projects that make use of Lifelines data are evaluated. Researchers will receive an invitation for filling out a short evaluation questionnaire during the execution of the project. Based on the results of these evaluations, Lifelines strives to continuously improve the services.

Publications

Researchers are obliged to publish the results of their research project in scientific journals or printed scientific meetings. Agreements on the use of the Lifelines and IADB.nl data and the rights/ obligations with regard to publications are described in the RMAA. If researchers have also used data from Statistics Netherlands, they must also follow [the agreements on publications of Statistics Netherlands](#).

Lifelines and IADB.nl should also be informed about upcoming publications and other news coverage of your research via the Lifelines Research Office (research@lifelines.nl) and IADB.nl office (info@IADB.nl). In this way we can prepare for any questions from the Lifelines participants and we can help you to share your research results with the general public via our website and / or social media.

Reference paper

The linked data from the Lifelines Cohort Study and IADB.nl database have already been used in a first study with the aim to assess the concordance of the self-reported medication use as collected by Lifelines with information of the prescription database IADB.nl. Please refer to this paper in your publications:

- Sediq R, van der Schans J, Dotinga A, Alingh RA, Wilffert B, Bos JHJ, Schuiling-Veninga CCM, Hak E. [Concordance assessment of self-reported medication use in the Netherlands three-generation Lifelines Cohort Study with the pharmacy database IADB.nl: The PharmLines Initiative](#). *Clinical Epidemiology*. 2018;10: 1-9.

Appendix A: Lifelines Review Criteria

Applicant

- Proposals can only be submitted by a senior (non-commercial) researcher. “Senior” is defined as holding a PhD degree or similar qualification.
- Applicant is currently active in research as shown by at least one publication in an international scientific journal during the last 12 months.

Application

- The application form is completed.

Quality

- It should be possible to write a scientific paper on the results.
- Unlike grant proposal reviews, it is not about the best proposal but about minimum scientific criteria: problem adequately described, research question clearly defined, approach that can answer this question.

Data

- The research question can be answered by the available data within Lifelines, IADB.nl and Statistics Netherlands.
- All requested data are needed to answer the research question(s) and match the proposal.
- When data is requested for which additional agreements are made with the researcher who is the intellectual owner or who has paid for the collection of the data, the appropriate actions as stated in the document ‘Additional agreements for data/material use’ are carried out towards this researcher and the applicant.

Legal and ethical issues

- There are no ethical issues to conduct the proposed research.
- In case data of children (<12 yrs) are requested, an employee of Lifelines should be involved in the Research Project.
- There must be no group privacy-issues.

Feasibility

- It is possible to grant access to the requested data through the regular processes.
- It is possible to establish the requested data linkage within a reasonable period of time.