PHIRI
Population Health Information Research Infrastructure

Mid-size prototype of PHIRI federated infrastructure

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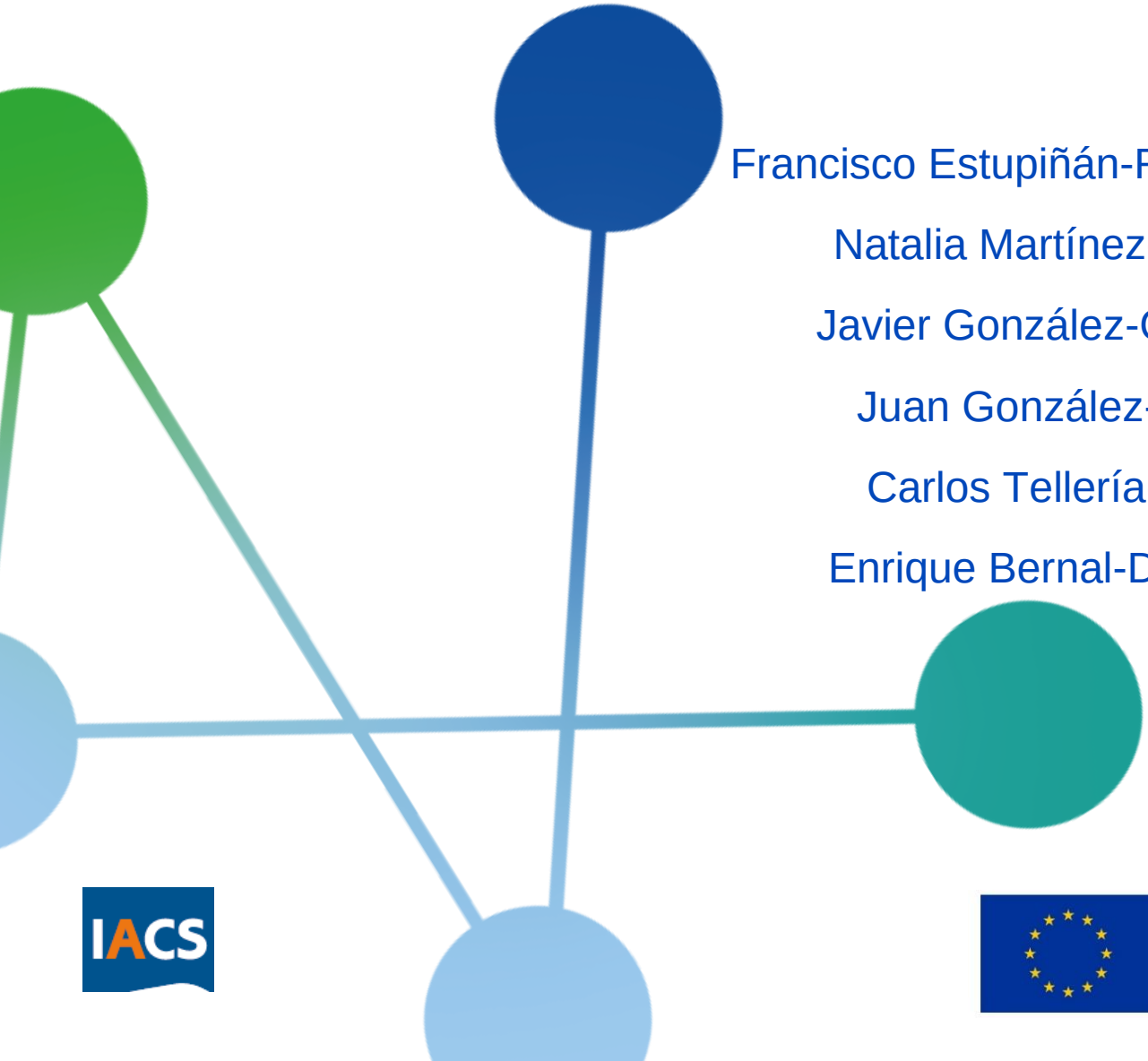

IACS

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Executive summary

PHIRI aims to facilitate and support open, interconnected, and data-driven research by sharing cross country COVID-19 population health information, and exchanging best practices related to data collection, curation, processing, use, and reuse following ELSI and FAIR principles. It has the objective: 1) to provide a Health Information portal for COVID-19 with FAIR catalogues on health and health care data, 2) to provide structured exchange between countries on COVID-19 best practices and expertise, and 3) to promote interoperability and tackle health information inequalities.

Within PHIRI WP7 has developed the technological substrate for the implementation of a federated research infrastructure that allows mobilizing sensitive data to respond multiple research queries in multiple sites, while preserving GDPR principles.

The task 7.1 demonstrated the suitability of this federated research approach in the production of accurate and timely research outputs for a rapid policy response on COVID-19; in particular, this task established the governance mechanism and implemented the technological solutions to respond to four uses cases carried out in multiple sites (countries). The following use cases took place:

1. Impact of the COVID-19 on health care in more vulnerable populations (Use case A).
2. COVID-19 related delayed care in breast cancer patients (Use case B).
3. Effects of the COVID-19 pandemic on maternal and newborn health (Use case C).
4. COVID-19 related changes in mental health care (Use case D).

Deliverable 7.1 (13/05/22) already contained features of the mid-size prototype of the PHIRI Federated Infrastructure to serve use cases that were already implemented at that point in time. Previously, we described the building blocks of the development of the medium scale (mid-size) PHIRI federated research infrastructure. This entails the development of a common data model for each of use case, the implementation of scripts for data quality assessment and analyses, all of them contained within a Docker Image. The Docker Image is a technological solution that is a secured environment for the implementation of the Federated Research Infrastructure (FRI) across nodes.

In Deliverable 7.2 (14/04/23) we complemented the development of the mid-size prototype of PHIRI Federated Research Infrastructure with the development of a demonstrator piloting the human-to-machine interface. This interface automatically builds an updated version of an international comparable report for use case B. This report is generated each time a partner completes the local analysis and shares their aggregated outputs.

An additional subtask 7.2 was to explore the use of the Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) to represent the information requirements specified in the use cases into a single harmonised common data model..

PHIRI Federated Research Infrastruture (FRI)

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THE ARCHITECTURE

The PHIRI federated architecture consists of a number of country **nodes (PHIRI partners)** acting as Data Hubs, and a **central orchestrating hub at IACS:** (1) The orchestrating hub develops, implements and shares the analytical pipeline and provides support to the federated research infrastructure for its deployment; (2) Nodes deploy the pipeline local analyses on their premises; (3) intermediate outputs (e.g., aggregated results or models) obtained from the local analyses are sent to the Central Hub, so, no sensitive data is shared across the federation of nodes but only digital objects; (4) the central hub can perform meta-analyses with those intermediate outputs if required.

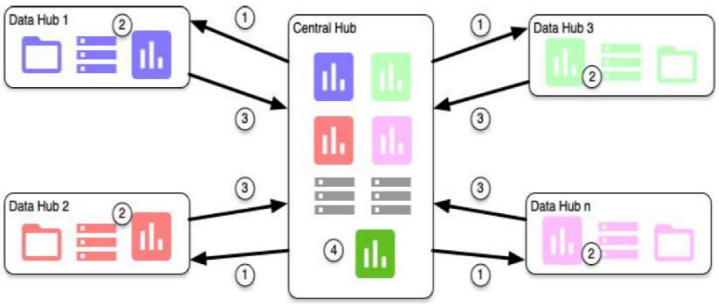

Figure 1 PHIRI federated architecture

PROTOTYPING THE ORCHESTRATION OF A USE CASE

The orchestrating hub has developed a prototype, a stepwise approach, aiming full interoperability at any stage of the process; thus, starting with the formalization of the research query as a common data model for all the nodes, following with the deployment of the analytical pipeline on-premise to run the analyses and, finalizing with the collection of the research results and their publication.

Figure 2 PHIRI workflow to build a reproducible analytical pipeline

This stepwise approach includes the following:

1. Formalising the Research Question,
2. Iteratively building a Common Data Model specification with the contribution of all participants in each research question,
3. Generating a synthetic dataset following the specifications of the agreed common data model,
4. Iteratively developing and testing the scripts (code) implementing the Data Quality Analysis using the synthetic data set, tailored to the quality requirements of the research question (i.e., following a fit-for-use approach to data quality assessment),
5. Iteratively developing and testing the scripts (code) of the statistical analysis using the synthetic data set. The study should implement the methodologies and analytical techniques enabling the response to the research question,
6. Deploying the use case (or research question) using a reproducible deployable solution (i.e. Docker) on-premise in each participant by distributing the common data model, the synthetic dataset (as data example), and the data quality analysis and statistical analysis script in a reproducible way, including the environment to run the analyses and all dependencies required to manage data and to reliable produce the expected outputs,
7. Collecting the local (on-premise) outputs produced by the local analysis of each participant to summarise them or meta analyse them by the promoter of the research question (or use case leader),
8. Finally, producing the deliverable based on the summary or meta-analysis of the collection of local outputs.

USE CASE OUTPUTS RECOLLECTION AND SYNTHESIS FOR DELIVERABLE PRODUCTION

The last step of the PHIRI federated pipeline is to collect, synthesise and compare the outputs of the local analysis run on-premise by each partner to produce insights derived from the international comparison analysis (or meta-analysis of the outputs). Therefore, outputs of the on-premises analyses are expected to be shared with the central hub to enable their synthesis and further analysis. These outputs are immediately and directly comparable across participating partners in a use case due to previous agreement in the input common data model, common scripting for the analysis and a systematic data processing using a common reproducible pipeline. All use cases integrated in the PHIRI app are expected to produce the same kind of outputs independently of their specificities. Those are a) an interactive report on the local analysis, providing immediate feedback for the participant partner for face validation and insight on the scope of the use case research question; b) an interactive data quality report (exploratory data analysis) providing information about the quality of the input data that might be required to better interpret the results; and, c) an aggregated output set that compiles the data required for further comparative analysis with other participating partners.

The communication of those aggregated datasets from the participating partner to the orchestration hub (*marked as (3) in Figure 1*) was originally done via direct email to each use case coordinator attaching a compressed file –the file could be encrypted depending on the requirements of the participant partner. This organizational setting was considered a pragmatical approach to communicate the local outputs, those being originally supervised by the partner producing them and not requiring further security measures due to being aggregated following the disclousure policy (*i.e., k-anonimity level*) agreed by partners participating in each use case. However, this human-to-human interaction does not facilitate the execution of the outputs synthesis or the meta-analysis of the aggregated data (*marked as (4) in Figure 1*) as it entails managing multiple asynchronous communications between participants and the orchestrating hub. Although practical for the implementation and production of the results expected from the use cases within WP6, this setting

was just conceived as a first step in developing and implementing a fully distributed research infrastructure within the PHIRI federation both at the organizational and the technical levels.

The step-wise approach towards the PHIRI federated research infrastructure entails the development and implementation of human-to-machine communication of the aggregated local outputs as a second step (tier 1 - *i.e., via automated reporting based on aggregated data update*); a machine-to-machine unique direction communication (tier 2 – *i.e., via an application programming interface (API) on the orchestration hub that could be leveraged by the PHIRI app after completing the local analysis to POST aggregated outputs in the orchestration server*); and finally a machine-to-machine bidirectional secure communication (tier 3 – *i.e., via establishing a secure communication channel between the orchestration hub and the participating data hubs enabling bidirectional messaging with script execution privileges within containarised environments*) (see Figure below).

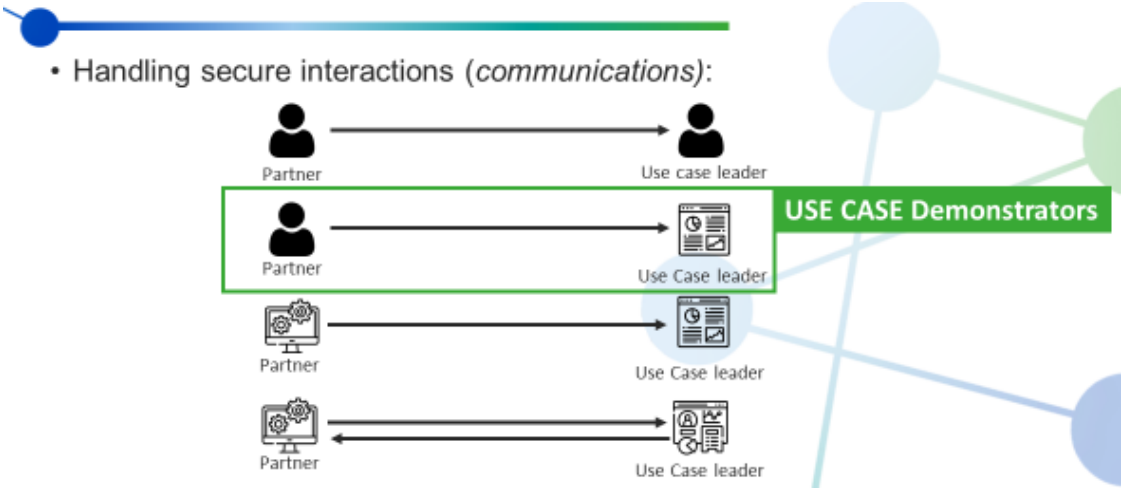

Figure 3 Step-by-step plan progressing towards a fully distributed PHIRI federated research infrastructure

- Handling secure interactions (*communications*):
  - TIER 0 – HUMAN to HUMAN interactions
    - Example*: Each participant partner execute the analyses and sends an e-mail with a) the data quality report and b) the aggregate data attached to the use case leader for each use case in which they are participating*
  - **TIER 1 – HUMAN to MACHINE interaction (with user interface)**
    - Example: *Each participant partner execute the analyses, **logs into a website (i.e. health information portal) with user authentication and upload** the data quality report and **the aggregated data** to enable further meta-analysis or comparison by use case leaders*
  - TIER 2 – MACHINE to MACHINE one-way (automating retrieval of the outputs)
    - Example: *Each participant partner execute the analysis and press "Send outputs" to submit the data quality report and the aggregated outputs to a common repository enabling further meta-analysis or comparison by use case leaders*
  - TIER 3 – MACHINE to MACHINE two-way (distributing algorithms – federated learning)
    - Example: *Each participant partner configures an environment where the required data is available for analyses, and manages authorization for the deployment and execution of analytical algorithms on their data and the authorization for sharing their outputs*

Figure 4 Step-by-step approach to handling secure interactions (i.e., communication) within PHIRI federated research infrastructure

MATERIALIZATION OF THE PROTOTYPE

The PHIRI Federated Research Infrastructure (FRI) is supported by a containerised reproducible solution for data analysis to be deployed on-premises by each participant partner. This solution (a Docker image) has been published in ZENODO (https://doi.org/10.5281/zenodo.5729310) and constitutes a small-medium scale prototype that includes all the pipeline components required to carry out the research queries foreseen in WP6 and the demonstration pilot (Version 2.2.1). The building blocks of the PHIRI infrastructure are:

1) **5 common data models**: one for both demonstration pilot and four referred to the WP6 use cases.

The common data models are the result of the formalization of the research queries included in these use cases in a way that is semantically interoperable for all the participant nodes. The research queries are the following:

a) Use case A Vulnerable populations, inequalities and risk factors with direct or indirect impact on health care outcomes during the COVID-19 pandemic: To clarify whether health care utilization patterns in vulnerable populations vary between settings and over time and is linked to the COVID-19 epidemiological situation, using individual level health record, administrative and research data combined with ecological/group level contextual data

b) Use case B COVID-19 related delayed care in breast cancer patients “Was there any delay in the treatment of breast cancer patients because of the COVID-19 stringency measures?”: Demonstrate whether has been any increase in surgical and/or co-adjuvant (i.e. radiotherapy, chemotherapy, hormonotherapy and immunotherapy) treatments delay because of the COVID19 crisis in eligible women diagnosed of breast cancer using individual level health record, administrative and research data combined with ecological/group level contextual data.

c) Use case C Effects of the COVID-19 pandemic on maternal and newborn health: Investigating the pandemic’s direct (infection by SARS-CoV-2) and indirect effects on perinatal health using routine population birth data, and assess whether effects differ by socioeconomic context.

d) Use case D COVID-19 related changes in population mental health: Measure changes in population mental health associated with the COVID-19 pandemic and, in particular, demonstrate whether has been any increase in healthcare utilisation of mental health treatments as a consequence of the COVID19 crisis in eligible patients diagnosed of depression and/or anxiety using individual level health record, administrative and research data combined with ecological/group level contextual data.

e) Demonstration pilot for rapid-cycle federated analysis. Piloting the federated analyses of the evolution of a number of indicators for the monitoring and surveillance of the COVID-19 pandemic (7-day reproductive number, 7- and 14-day incidence rates, regular and ICU admissions, bed occupancy rates) and 7- and 14-day predictions, using individual data from a number of data sources -COVID-19 monitoring and surveillance registries, hospital data, and administrative data.

The latest version of the common data models can be found here:

WP6 - Use Case A Common Data Model https://doi.org/10.5281/zenodo.5148013; (v3.0.0)

WP6 - Use Case B Common Data Model https://doi.org/10.5281/zenodo.5148021; (v2.0.0)

WP6 - Use Case C Common Data Model https://doi.org/10.5281/zenodo.5148031; (v2.0.1)

WP6 - Use Case D Common Data Model https://doi.org/10.5281/zenodo.5148039; (v2.0.0)

WP7 – Pilot Common Data Model https://doi.org/10.5281/zenodo.5148466; (v1.0.0)

2) **Synthetic datasets** for the variables included in the data model – these synthetic data set are used to fine tune the data quality assessment scripts and the analytical algorithms before deployment on-premise

3) **Data quality assessment scripts** Once the data required in each use case, has been obtained and transformed to the common data model in each of the participating nodes, the data quality assessment script will help to understand the quality of the dataset that the researcher is going to use – in particular, completeness of each of the variables, anomalous distributions, the existence of numerous outliers, etc. For all use cases data quality assessment reports are customized using pandas-profiling functionalities from the 'panda' library in Python v.3.10.

4) **Algorithms for data analysis** scripts for the PHIRI use cases A to D. Once the dataset has been accepted by the researchers (ie, the data quality assessment provided recommends to follow), the analytical scripts are run to produce the actual research results. Updated versions of the analytcal algorithms can be found here:

WP6 – Use Case A scripts (R Markdown) https://doi.org/10.5281/zenodo.6359850; (v1.1.2)

WP6 – Use Case B scripts (R Markdown) https://doi.org/10.5281/zenodo.6359892; (v4.0.1)

WP6 – Use Case C scripts (R Markdown) https://doi.org/10.5281/zenodo.6380733; (v2.0.1)

WP6 – Use Case D scripts (R Markdown) https://doi.org/10.5281/zenodo.6359904; (v1.1.1)

WP7 – Pilot scripts (R Markdown) https://doi.org/10.5281/zenodo.7092521 (v1.0.0)

(Nota bene: Rapid-cycle analysis is enabled through continuous data updates by participant partners deploying this prototype)

5) **Mappings** from Use case A, B and D common data models to OMOP v5.3 CDM have been included as part of the update of the PHIRI app to mid-size prototype [check at https://doi.org/10.5281/zenodo.5729310], although they have not been integrated within the analytical pipeline as complete mapping at the variable level. The original idea of representing the use cases' information requirements into OMOP CDM was not possible due to semantic constraints in OMOP to represent certain variables required in the use cases within the scope of population health science.

Thus, a mapping exercise was completed between the CDM for use cases A, B and D to OMOP CDM, both at variable and value levels. Results from this mapping exercise are commented within this Deliverable, and mappings from use case A, B and D common data models to OMOP CDM v5.3 variables and values are included in the update of the mid-size prototype of PHIRI Federated Research Infrastructure (Deliverable 7.2) in Zenodo. A complete mapping between the use cases data models and OMOP CDM was not possible at the variable level due to constraints regarding variable definitions (*i.e., semantics*) and data types (*i.e., syntaxis*) and the overall rationale of the use cases design (*i.e., population health research*) versus OMOP design guiding principles (*i.e., pharmacoepidemiological research*). However, mapping was possible at the value level mainly using OMOP-valid standard codes following a comprehensive approach. These incompatibilities between PHIRI and OMOP CDMs do not preclude the possibility of recreating –totally or partially- the cohorts defined to answer the research questions posed by PHIRI use cases using OHDSI-OMOP cohort definition based on OMOP value codes. It instead showcases the existence of two different approaches to semantic and syntactic interoperability to enable secondary use of healthcare, both aimed to facilitate reproducible pipelines and replicable outputs, with a) PHIRI approach, driven by the materialization of a specific research question in a bespoke data model, enabling broader participation (*only depending on data availability and accessibility*), data minimization (*enabled at both data source selection and entity, variable selection*), comparative analysis (*i.e., via synthesis of*

local outputs, or meta-analysis), and enabling linkage with compatible area-level data (*i.e., using standard area level categories such as NUTS*); or b) OHDSI approach, driven by a standard design, only accessible upon the extraction, semantic mapping and transformation of all data sources available to a standard data model (OMOP CDM), tying research question specification to the semantic constraints of the standard model specification.

6) **Demonstrator of the human-to-machine interface** enabling automatic update of the interactive use case B international comparison report. Technical specifications of the demonstrator are provided as part of this document (*Annex 2*). The containerarised application supporting the use case B demonstrator is deployed in IACS servers managed by the Biocomputing Unit (Aragon, Spain). The demonstrator (Use Case B) can be accessed via links in the Health Information Portal within the menu tab for 'Federated Demonstrators' (https://www.healthinformationportal.eu/services/federated-demonstrators) or directly at a) https://phiri.iacs.es/upload for the 'Upload' interface -to upload new aggregated outputs from the local analysis procuded by a partner participating in use case B, b) at https://phiri.iacs.es/report for the 'Interactive report' on internacional comparison analysis of participants in use case B, and c) at https://phiri.iacs.es/ for an interactive mockup of the web application interface enable upon PHIRI app local deployment in a partners' systems.

Annex 1 Technical specifications

Current technical stack of the PHIRI FRI includes (x2) Docker containers, using:

- (x1) Server-side (Back-end)
  - Framework: Nest (NestJS) -> TypeScript (https://nestjs.com/)
  - Execution environment: Node.js® >= v14.0.0 (https://nodejs.org/es/)
  - Database management system: SQLite (https://www.sqlite.org/index.html)
  - Data analysis environment: R version 4.0.4 (https://www.r-project.org/)
  - Data wrangling and management: Python (>= Python 3.8.12 (https://www.python.org/))
- (x1) Client-side (Front-end Web application)
  - Web server/proxy: Nginx (https://www.nginx.com/)
  - Framework: Vue.js -> HTML, CSS, and JavaScript/TypeScript (https://vuejs.org/)

Requirements for installing Docker

The PHIRI FRI includes deployment instructions as a PDF document ("deploy_phiri_app.pdf").

General requirements for installing Docker (support):

- Server: 1 server (or VM)
- CPU: 1 CPU minimum (or 2 CPU for VM configuration)
- GPU: No dedicated GPU required
- RAM Memory: 4 GB minimum (8 GB recommended)
- OS: Unix based (Linux or other) with Docker support

Specific PHIRI FDI Docker deployment requirements

- RAM Memory: 8 GB minimum (16 GB recommended)

Annex 2 Technical specifications of the demonstrator (Use Case B)

Current technical stack of the Demonstrator includes (x1) Docker container, using:

- (x1) Server-side (Back-end)
  - Framework: Wildfly v.16 (https://www.wildfly.org/)
  - Execution environment: Java, Java Runtime Environment (JVE), Java Persistance API (JPA) (latest versions - https://www.oracle.com/java/)
  - Database management system: PostgreSQL (https://www.postgresql.org/)
  - Data analysis environment: R version 4.1.0 (https://www.r-project.org/)
  - Interactive reports: Quarto version 4.2.0 (https://quarto.org/)
  - Data wrangling and management: Python (>= Python 3.8.12 (https://www.python.org/))
  - Web server/proxy: Nginx (https://www.nginx.com/)

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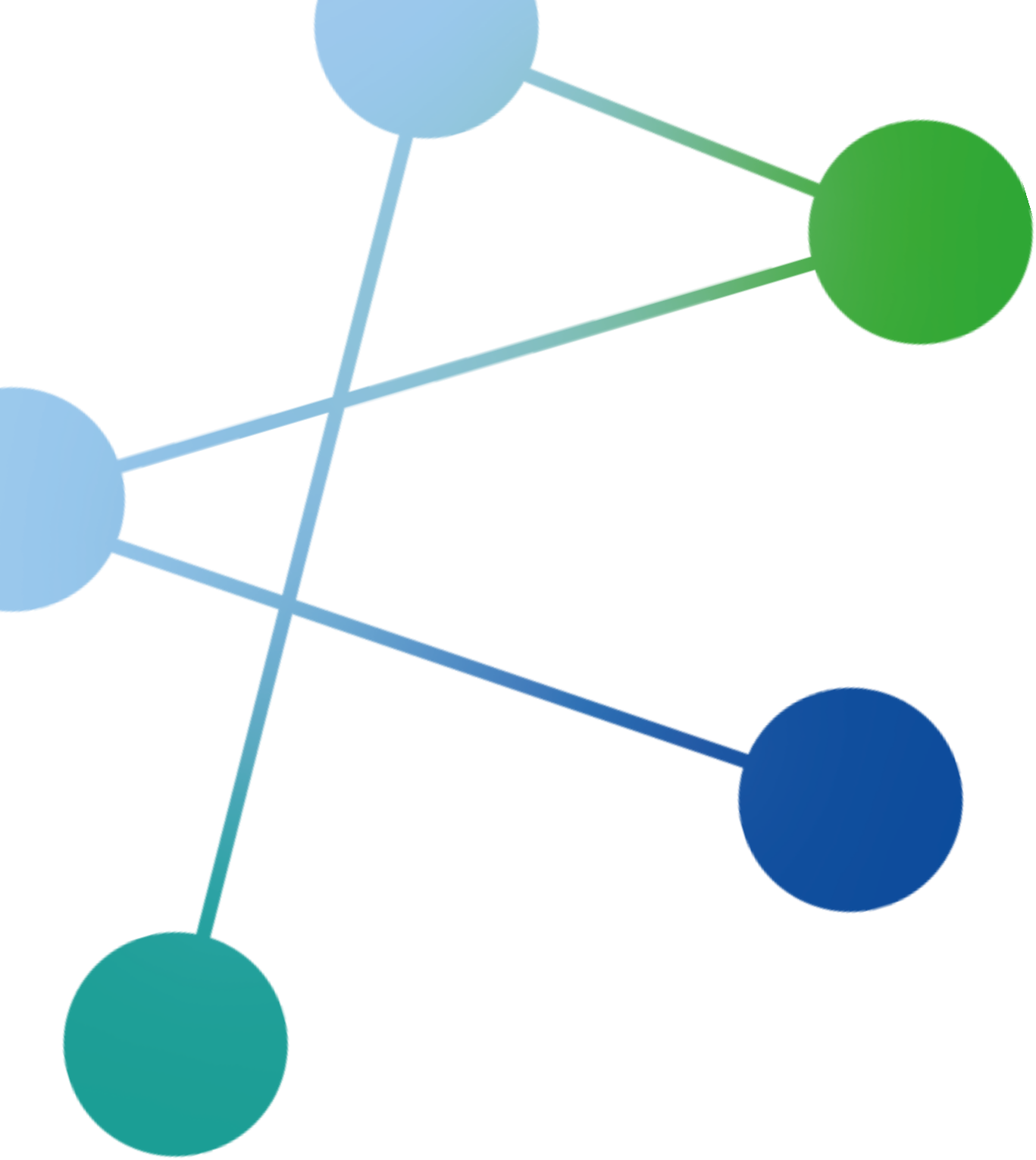

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