xShare

Expanding the European EHRxF to share and effectively use health data within the EHDS

WP5

D5.3 Proposed interoperability specification for an International Patient Summary for Research mapped to international standards

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Der blev ikke fundet nogen elementer til indholdsfortegnelsen.

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List of Abbreviations

All abbreviations included here can also be found in the xShare online glossary: https://glossary.ramit.be/public/home.cfm?pid=11

Abbreviation	Term
API	Application programming interface
AE	Adverse event
CDASH	Clinical Data Acquisition Standards Harmonization
CDASHIG	Clinical Data Acquisition Standards Harmonization Implementation Guide.
CDE	Common Data Element
CDISC	Clinical Data Interchange Standards Consortium
CDISC SDTM	Clinical Data Interchange Standards Consortium study data tabulation model
CDMH	Common Data Model Harmonization
CDW	Clinical Data Warehouse
CT	Clinical trial
EC	European Commission
eCRF	Electronic case report form
EHRxF	(European) Electronic Health Record exchange Format
EHDS	European Health Data Space
EHR	electronic health record
EMR	Electronic medical record
FDA	Food and Drug Administration of the United States
FHIR	Fast Healthcare Interoperability Resources
FHIR IG	FHIR implementation guide
HHS	US Department of Health and Human Services
HID	Health information domains
HL7	Health Level Seven International
IG	Implementation guide
IHE	Integrating the Healthcare Enterprise
IHI	Innovative Health Initiative
IPS	International Patient Summary
IPS+	International Patient Summary plus for research and public health
ISO	International Organisation for Standardization
JSON	JavaScript Object Notation
LOINC	Logical Observation Identifiers Names and Codes
MedDRA	Medical dictionary for regulatory activities
NIH NCI EVS	National Institutes of Health – National Cancer Institute Enterprise Vocabulary Services.
OHDSI	Observational Health Data Sciences and Informatics

OMOP	Observational Medical Outcomes Partnership
ONC	Office of the National Coordinator for health information technology
PhPID	pharmaceutical product identifier
PHR	Personal Health Record
RWD	Real world data
SAE	Serious adverse event
SDTM	Study Data Tabulation Model
SNOMED	Systematized Nomenclature Of Medicine
STU	HL7 standard for trial use
TA	Therapeutic Area
UDP	HL7 Vulcan Utilizing the Digital Protocol
USCDI	US Core Data for Interoperability
USDM	Unified Study Definitions Model
WHO	World Health Organisation
WP	work package
XML	extensible markup language

Executive summary

This deliverable, D5.3, is the third in a series produced by work package 5 of the xShare project. It presents the technical specification for an extended version of the International Patient Summary (IPS+) that increases the value of the ISO published IPS for secondary uses, in particular for clinical research and for public health. It builds on the results of two previous WP5 deliverables. D5.2 provides a detailed analysis of the most likely use cases that could be adopted by the clinical research community to leverage the value of the wide scale availability of standardised computable health summary information about the citizens within each European country, to improve the design, accelerate recruitment and reduce redundancy of data collection in clinical trials. D5.1 critically examines the content of this summary information, anticipated to align with the ISO IPS, against the results of research over the past decades that have highlighted the data elements of greatest value to these clinical research use cases. It just slightly extended IPS, the IPS+, that combines maximum value for continuity of patient care with maximum value for research and public health.

This deliverable defines the technical specification of the IPS+. It provides the representation of the data elements utilising the HL7 FHIR Implementation Guide for the IPS, as a project specific version incorporating the additional data elements. The specification provides the mappings of terminological concepts and value domains to SNOMED CT. It also provides the detailed correspondence of the data element names and value domains to CDISC SDTM.

These representation and mapping resources are hosted online to enable them to be used in computable format by implementors of systems and tools that will enact these use cases. This deliverable therefore briefly introduces each one and provides a link to the supplemental materials.

The specification provided in this deliverable is an initial version, developed by experts in these different standards. It is intended to be used during 2025 by several demonstrators that will seek to implement and test data flows and data transformations corresponding to one of the use cases in D5.2, or potentially to another similar use case. A second version of this deliverable specification will be published in the winter 2025-26 as an update, benefiting from the experience of those implementers. It is intended for the final technical specification to be offered as a proposal for adoption by the European Commission as part of its overall specification of the European EHRxF.

1 Background to this specification

This deliverable, D5.3, is the third in a series produced by work package 5 of the xShare project. It presents the technical specification for an extended version of the International Patient Summary (IPS) that increases the value of the ISO published IPS for secondary uses, in particular for clinical research and for public health.

The xShare project as a whole focuses on the delivery and promotion of value from the anticipated wide scale uptake of the European Electronic Health Record exchange format (European EHRxF) through the adoption across Europe of the European Health Data Space Regulation. xShare places particular emphasis on patient empowerment because the Regulation makes special provision for patients to be able to access their summary information and to have the authority to enable other actors to access this. WP5 looks specifically at the value of this exchange format for clinical research, in particular for the design and conduct of clinical trials that are sponsored by the pharmaceutical industry for regulatory submission.

WP5 takes the view that each European country, at national or regional levels or both, will need to consolidate European EHRxF data sets on its populations in relatively high-performance platforms, which have been exported from GP and/or hospital EHR systems. These large-scale clinical document repositories will be required in order to enable rapid response to any cross-border request for the summary of one of their citizens in case of an urgent health need whilst the citizen is in another European country. It is very likely that this investment in the European cross-border capability will also be utilised within border, whenever a patient needs to be treated by an unfamiliar healthcare provider who has no historic records on the patient. These repositories could also be used for population level queries to verify the size and distribution of a potential recruitment pool of patients meeting clinical trial protocol eligibility criteria. They could potentially be used for site selection if it is permitted to discover which healthcare sites are actively treating eligible patients. These analyses could be undertaken on anonymised data. A further and important scenario is for patients themselves to propose their participation in a potentially relevant clinical trial, because they will have access to their exchange format data and the capability to forward this to a trial centre for consideration (effectively for pre-screening).

An earlier WP5 deliverable, D5.2 Analysis of business use cases for use of European EHRxF HIDs in clinical research, elaborated on these possible scenarios of use with detailed use cases, data flows and success conditions. These use cases are summarised in Chapter 3 of this deliverable, for the convenience of the reader, but it is recommended that D5.2 is consulted for additional details on them.

Another earlier deliverable, D5.1 Proposal for a harmonized core data set across health care, population health and clinical research, specifies the recommended extension to the IPS to optimise its value for clinical research and population health. This deliverable consolidates the data element inventory identified by several international initiatives that have already screened multiple clinical research protocols in order to identify the commonly occurring, therapeutic area independent, data elements that represent eligibility criteria. The research also considered the most commonly required data elements for collection during clinical trials. The consolidated dataset was compared with the ISO IPS Data element inventory, in order to propose an extended version, the IPS+, that adds a modest number of data elements to the published standard whilst significantly increasing its research value. That deliverable provided the inventory of data elements, summarised briefly in Chapter 4 of this deliverable. However, readers intending to use this deliverable are recommended to read D5.1 first.

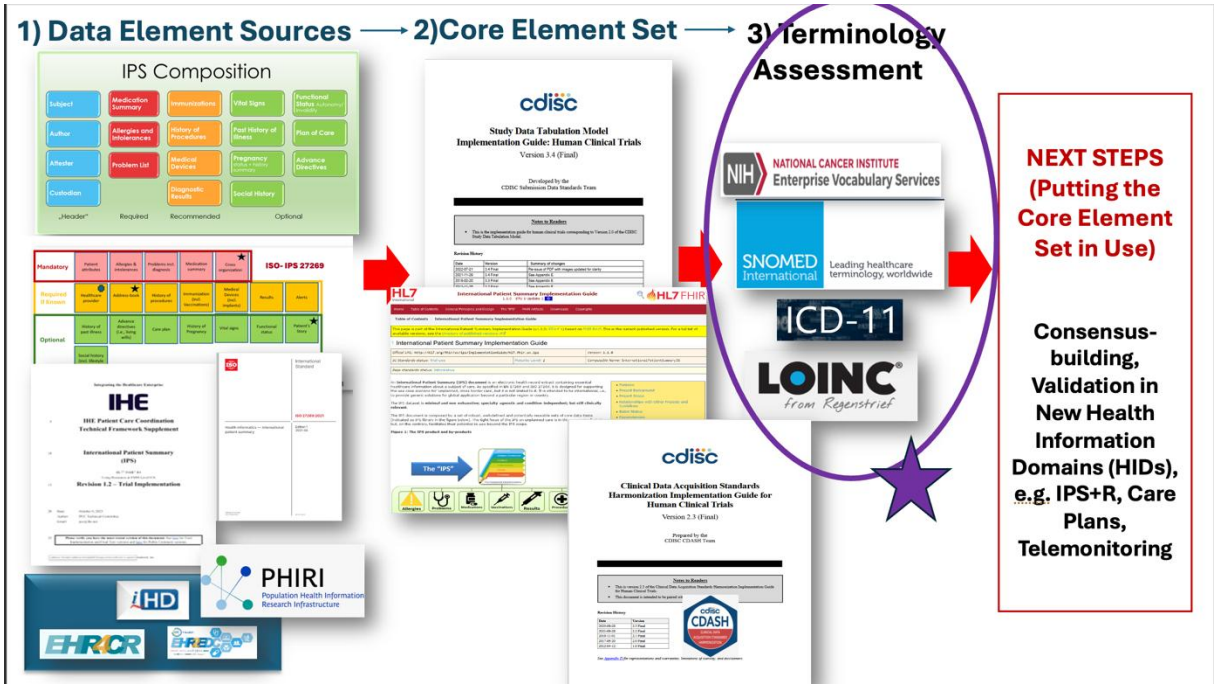

Figure 1: Diagram showing the progression of detail from D5.1 to D5.3.

The positioning of this deliverable as a progression from D5.1 is shown in Figure 1. It defines the technical specification of the IPS+. The challenge it aims to solve is the variability and semantic differences in health data. Addressing this issue will help create a consistent and reliable health data system, improving public health and wellness. It will also give individuals greater control over their health data and support seamless data exchange for both primary and secondary use.

2 Purpose of this specification

The purpose of D5.3 is to present how to use the International Patient Summary for secondary data purposes, such as clinical research and public health. This will improve the usability, the quality, and the timing of the data availability for these purposes. It is important to use secondary data efficiently to improve processes and reduce documentation burden. This guide provides detailed instructions for implementing business use cases, interoperability specifications aligned with international standards, and a standardized core data element set for use across healthcare, population health, and clinical research. To ensure consistency with existing terminologies, we include preferred value sets and code lists.

The specification is primarily in the form of downloadable resources to aid functionalities related to the xShare Yellow Button in support of secondary data use.

This document specifies the representation of the data elements utilising the HL7 FHIR Implementation Guide for the IPS, as a project specific version incorporating the additional data elements. The specification provides the mappings of terminological concepts and value domains to SNOMED CT. It also provides the detailed correspondence of the data elements names and value domains to CDISC SDTM. These mappings are required because the D5.2 use cases connect the domains of clinical research and healthcare, which (historically and currently) utilise different standards. Clinical trial critical eligibility criteria are likely to be expressed using CDISC standards, or could readily be mapped to them. EHR systems currently adopt varying standards or sometimes no standards for data representation, and are likely to be mapped by national eHealth programmes to HL7 FHIR and SNOMED. Any party seeking to transform queries containing clinical trial eligibility criteria will therefore need to perform this mapping from CDISC to HL7 FHIR & SNOMED. Similarly, any parties seeking to utilise a patient's IPS+ within a clinical trial for research data sets will need to perform the mapping in the other direction. This is illustrated in Figure 2.

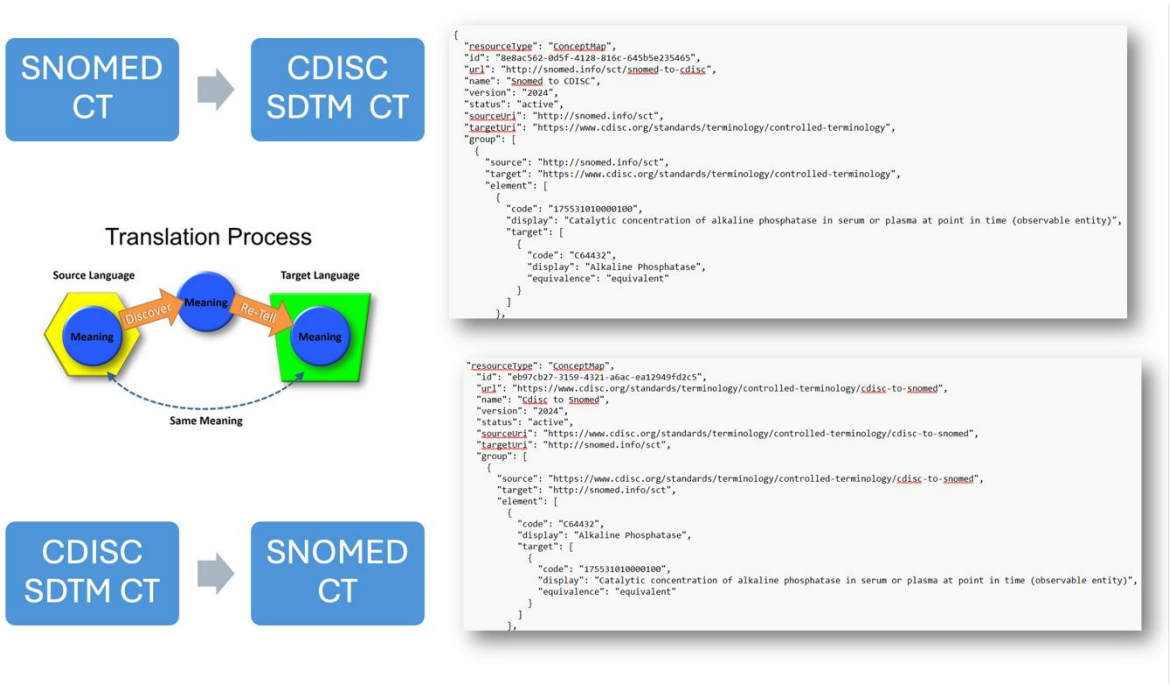

Figure 2: Diagram showing the progression of detail from D5.1 to D5.3.

The specification provided in this deliverable is an initial version, developed by experts in these different standards. It is intended to be used during 2025 by several demonstrators that will seek to implement and test data flows and data transformations corresponding to one of the use cases in D5.2,

or potentially to another similar use case. The authors of this deliverable will provide guidance to supplement this specification to those implementers. They will note areas of challenge, modifications needed to the specification and any areas of additional explanatory guidance that were needed. A second version of this deliverable specification will be published in the winter 2025-26 as an update, intended for wider piloting.

It is intended for the final technical specification to be offered as a proposal for adoption by the European Commission as part of its overall specification of the European EHRxF, and submitted to the by JIC IPS Coordination Committee for a future version of the IPS.

3 Business use cases for the IPS+ in clinical research

This chapter summarises, for the convenience of the reader, the main business use cases for clinical research that can take advantage of the future wide European adoption of the IPS+. The full details of these use cases are given in deliverable D5.2, which the reader is encouraged to review before adopting the specification presented in this deliverable.

In clinical research, the IPS+ can be used to assess study and protocol feasibility by ensuring sites have a sufficient patient population that meets the eligibility criteria as defined in the inclusion and exclusion criteria. It also aids in patient pre-screening by allowing patients who believe they might be eligible to share their data with potential study sites. Additionally, it supports the conduct of the study by enabling the transfer of data from EHRs/PHRs to Study Database Systems or EDC systems, which eliminates data duplication and improves data quality by avoiding content re-entry into an additional source and reduce burden on study sites personnel.

The D5.2 user stories emphasize the importance of patients being active participants in this process, by triggering the use case, through data sharing in accordance with GDPR portability rights. They also emphasize the need for follow-up after data sharing until effective inclusion in a clinical trial. The xShare Yellow Button data sharing functionality would benefit from a toggle feature, allowing patients to control their health data sharing.

For the research team and clinical investigators, efficient, relevant data sharing is crucial to streamline processes, minimize screen failures and save time.

Patients would benefit by receiving feedback[1] regarding their potential eligibility for a clinical trial through communication between the pre-screening tool and any application used by the patient to submit their enquiry, including compatible clinical trials and their locations. Location details help patients choose a hospital based on their preferences. For example, a patient participating in a prospective observational or a retrospective study would prefer a nearby hospital, while a patient seeking innovative drug treatment for an untreatable condition might be willing to travel further. For patients participating in clinical trials, this allows improved patient safety and for patients in general, faster access to new medications.

It is recognised that patients can benefit from being able to access and possibly download an identifiable data copy of the data captured during their trial participation, which goes beyond the scope of the IPS+ by covering a much wider range of data elements, sometimes quite specialised disease specific ones. This functionality is beyond the scope of this project, but is being tackled by other European projects, in particular IHI Facilitate (https://facilitate-project.eu/).

The business use cases summarised below, from D5.2, focus on clinical research. The design of IPS+ has also included important inputs from xShare WP4, and the data specification reported here additionally supports public health use cases and use in tackling cross-border health threats such as a future pandemic. The implementation of those use cases, including if they will utilise identifiable data for contract tracing or anonymised data for population surveillance, are beyond the scope of this deliverable.

3.1 Use case 1: study/protocol feasibility

The protocol designer composes a query taken from the eligibility (inclusion, exclusion) criteria for the trial, mapped from CDISC representation to the European EHRxF format, for execution as federated queries on IPS+ health data repositories. The aggregated candidate protocol eligibility criteria are used to discover the frequency distributions of potentially eligible participants across a network of hospitals

[1] Note: this feedback from the trial centre is not part of the data flow within this use case

within one or multiple countries (see Figure 3). It should be noted that this use case benefits from the anticipated consolidation by Member States of patient summaries and other European EHRxF data obtained via the EHDS primary use services, but the reuse within this use case is not within the terms of the EHDS secondary use services, but reuse in a conventional way if permitted by each Member State. A third-party Information and Communication Technology (ICT) platform company may facilitate this. This enables the identification of favourable sites for study participant recruitment.

The Trigger: Multi-stakeholder endorsement of the xShare IPS+ specifications as correct, relevant, practical and useful for the future of healthcare, treatment innovation and health systems sustainability. Note: unlike the use case below, individual patients are not consulted about or involved in these data flows, as only aggregated population level data is used.

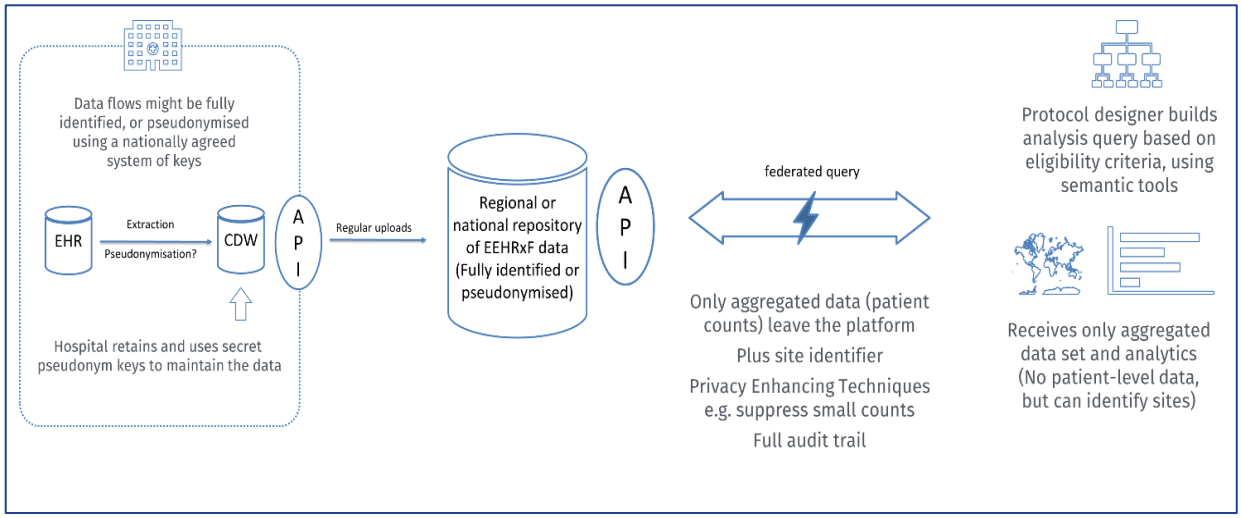

Figure 3: Study/Protocol Feasibility Workflow (reproduced from D5.2)

(CDW = Clinical Data Warehouse, EEHRxF = European EHRxF)

3.2 Use case 2: Individuals share data for potential study participation

Individuals explore potential clinical studies by leveraging their health data through a PHR that has been populated with up-to-date IPS+ data via the xShare Yellow Button. This use case implies interaction with study registries where there is a link between the open clinical trial, the hospital participating in the trial and a pre-screening tool. This link can be performed by the pre-screening tool (IT vendor). It also implies the mapping of health data from the IPS (presumed to be HL7 FHIR and SNOMED) to the pre-screening tool questionnaire (presumed to be CDISC) e.g. subject demographic = age, the patient must be between 18 and 75 years old to participate. Once the detection of a potentially compatible clinical trial with the patient or healthy volunteer, a percentage match is calculated for the citizen and investigator to determine how compatible they may be with clinical trials (e.g. the pre-screening is 80% compatible with the study eligibility criteria, the remaining 20% is unknown data such as non-IPS+ data). The on-site team would only be able to complete and evaluate the full patient pre-screening via a more detailed record exchange or by seeing the patient. The patient/healthy volunteer can therefore share their non-medical personal data with a hospital participating in the compatible trial. The hospital's research team can then contact the patient/healthy volunteer for more comprehensive screening. This workflow is shown in Figure 4.

The Trigger: A citizen wants to know if they are possibly eligible for a clinical trial.

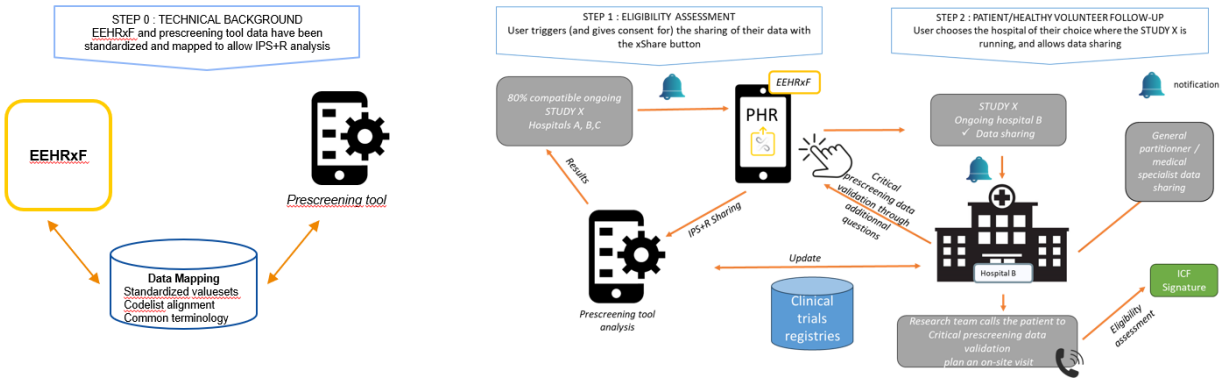

Figure 4: Participant volunteer pre-screening flow (reproduced from D5.2)

Note: In this figure a former term IPS+R is used, now referred to in this deliverable as IPS+.

3.3 Use Case 3: Study support PHR/EHRs to Study Database System or Electronic Data Capture (EDC)

This use case leverages existing IPS+ health data to support data collection defined in a health study (clinical study, epidemiological study) for enrolled patients, where the selection criteria were verified and the appropriate consent for data management (including IPS+ data access) was granted to meet regulatory requirements and local policies. Data collection leverages the European EHRxF via the implementation of the xShare Yellow Button (see Figure 5).

Citizen health data is present in EHR and PHR systems, and in Clinical Data Warehouses, Patient registries, Diseases networks, FAIR data repositories, etc. This data may be extremely helpful in supporting clinical research by reducing redundant data capture and increasing data quality in relation with the accountability of each information assigned to their respective sources in provenance management.

The Trigger: The patient or clinical trial investigator wants to send Study X data.

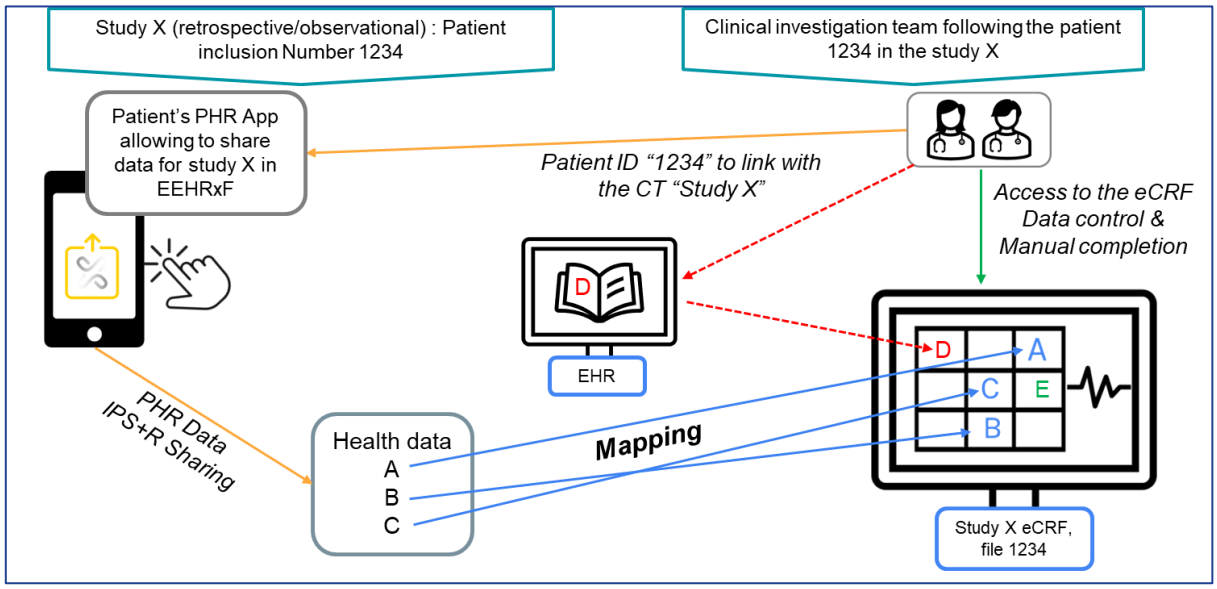

Figure 5: Study support – PHR/EHRs to EDC flow (reproduced from D5.2)

4 Overview of the IPS+ content

Figure 6 provides a view of the data elements recommended in D5.1 for the content of the IPS+. These are the results of substantial desk research and analysis across multiple data element lists derived by European and US projects to prioritise those that are most often included within clinical trial protocols. This work was supplemented by engagement with the public health work package in xShare, which has determined the data elements of greatest value for several of its use cases.

The data element concepts are provided with the CDISC Domain and the equivalent IPS Category. The data elements in white are currently present within the IPS. The data element concepts in black are supplementary, proposed to support clinical research and public health. Note these are Research Subject Identifier, Research Study Identifier, Adverse Event data element concepts and Healthcare Encounter data element concepts.

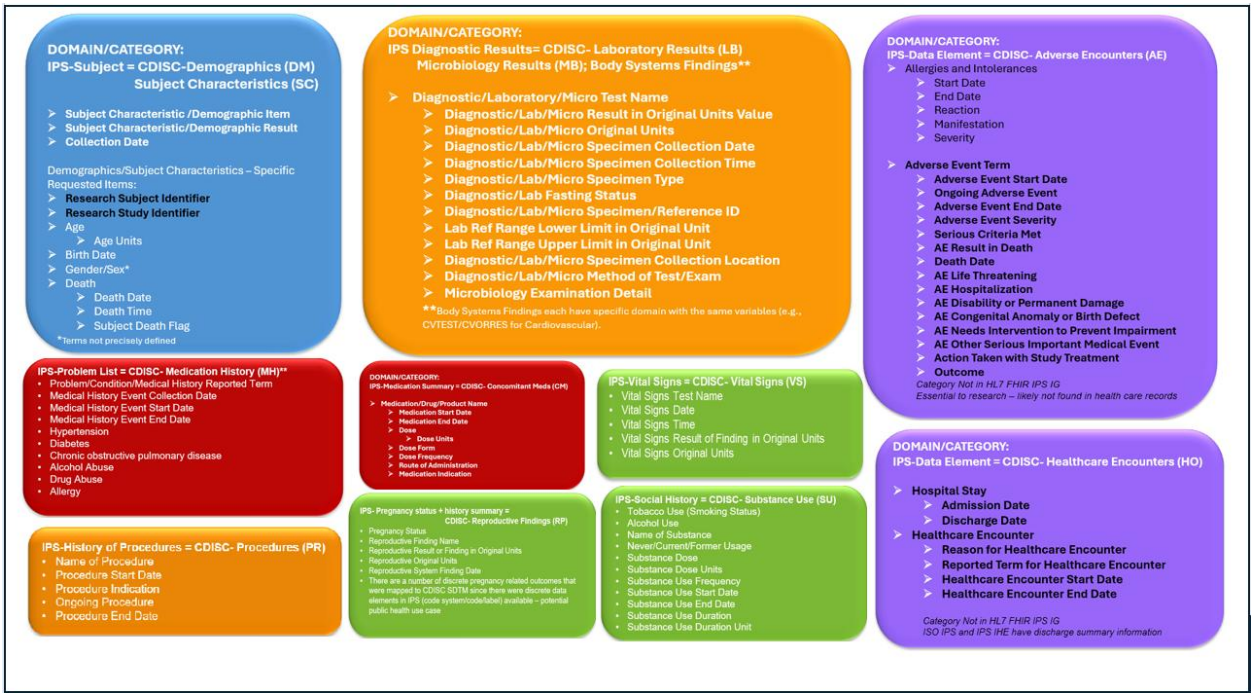

Figure 6: xShare Core Harmonised Data Elements (reproduced from D5.1)

4.1 Comparing Adverse Event with Allergies and Intolerances

Adverse Events in prospective studies are new conditions after trial enrolment and would likely be collected in EMR/EHR/PHR systems as Conditions. It is the timing of the events that deem them Adverse Events. Thus the "Allergies and Intolerances" section and "adverse event" data proposed in the IPS+ are very relevant to a prospective and interventional clinical trial, such as the evaluation of the efficacy and safety of a new treatment. The collection of adverse events, one of the most important parts of patient follow-up in a health study, is ensuring participant safety by evaluating and qualifying clinical parameters like adverse events (AE) and serious adverse events (SAE).

According to regulations, an AE is any undesirable experience associated with the use of a medical product in a patient and will be classified as serious under certain conditions:

- Linked to death or is life-threatening

- Implies hospitalization (initial or prolonged)
- Generates disability or permanent damage, congenital anomaly/birth defect
- Requires intervention to prevent permanent impairment or damage (devices)

In the case of a SAE for a drug/device trial a report must be produced to assess the impact of the trial (medication, follow-up, etc.) on the event and implement necessary measures to ensure participant safety. The SAE form must contain the diagnosis, start date, status (ongoing or closed), conclusion after the event, gradation, reason for classification as an SAE, causality, and action taken, all of which are included in the IPS+. Automating the SAE filling in the eCRF through European EHRxF in this use case would significantly improve patient safety in clinical trials.

If new occurrences of conditions or allergies arise in the patient, even during a clinical trial, these data would also be entered in an EHR as new conditions and allergies using its usual data elements. Therefore, in terms of mapping, these additional data element concepts specified for Adverse Events will likely be documented only on the research side and the full Adverse Event data element set does not need to be added to the IPS. Thus, the only additional concepts not in the current IPS are Research Subject, Research Study and the Healthcare Encounter data element set.

4.2 Mappings between CDISC standards and HL7 FHIR

One possibility to facilitate implementation of mapping data, the CDISC eCRF Portal has ready-to-use, CDASH compliant, annotated eCRFS available to import to systems. The CDASHIG provides the underlying mapping for transformation from CDASH to SDTM and is also available in machine readable format in the CDISC Library. These tools can be leveraged alongside the FHIR to CDISC mapping documents to provide a path towards going from FHIR IPS to the CDISC SDTM specification. Note that CDISC uses MedDRA codes, whereas the IPS is assumed to use SNOMED CT. A SNOMED CT to MedDRA mapping is maintained and published by SNOMED International (https://www.snomed.org/maps). Leveraging the FHIR to CDISC maps, the value sets provided that are aligned with the CDISC terminology will assist in providing support for PHRs that can be leveraged for secondary data use. These mappings are illustrated for medical history in Figure 7 and Figure 8.

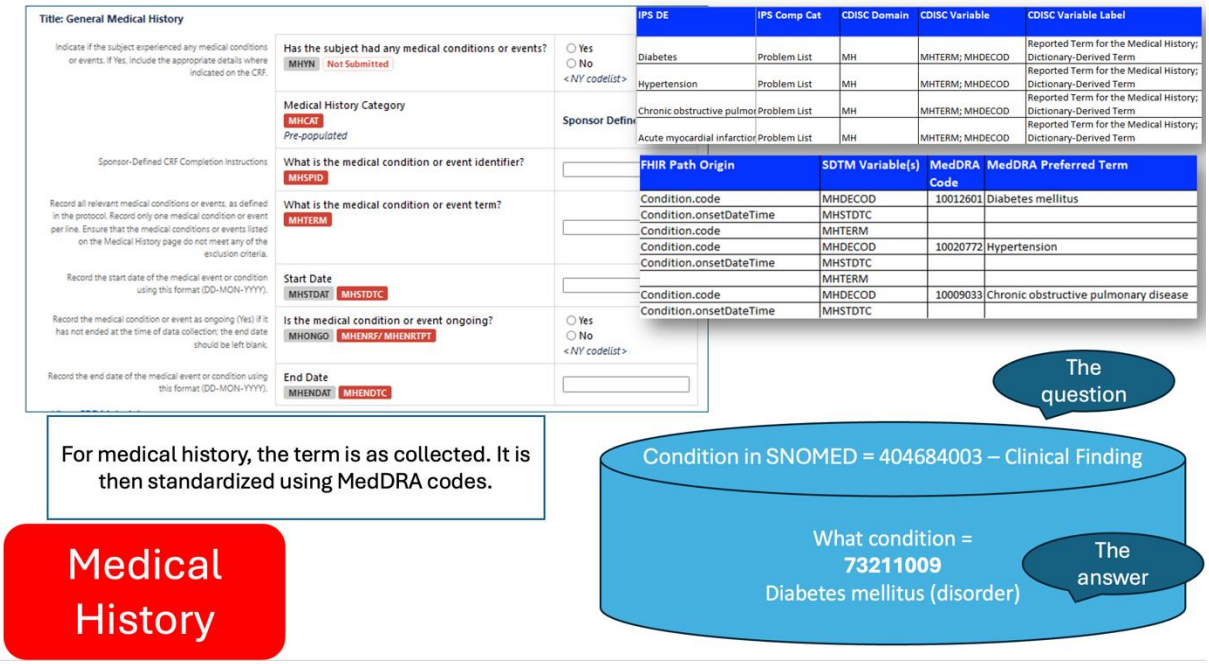

Figure 7: Mapping illustration for medical history between HL7 FHIR, SNOMED and CDISC

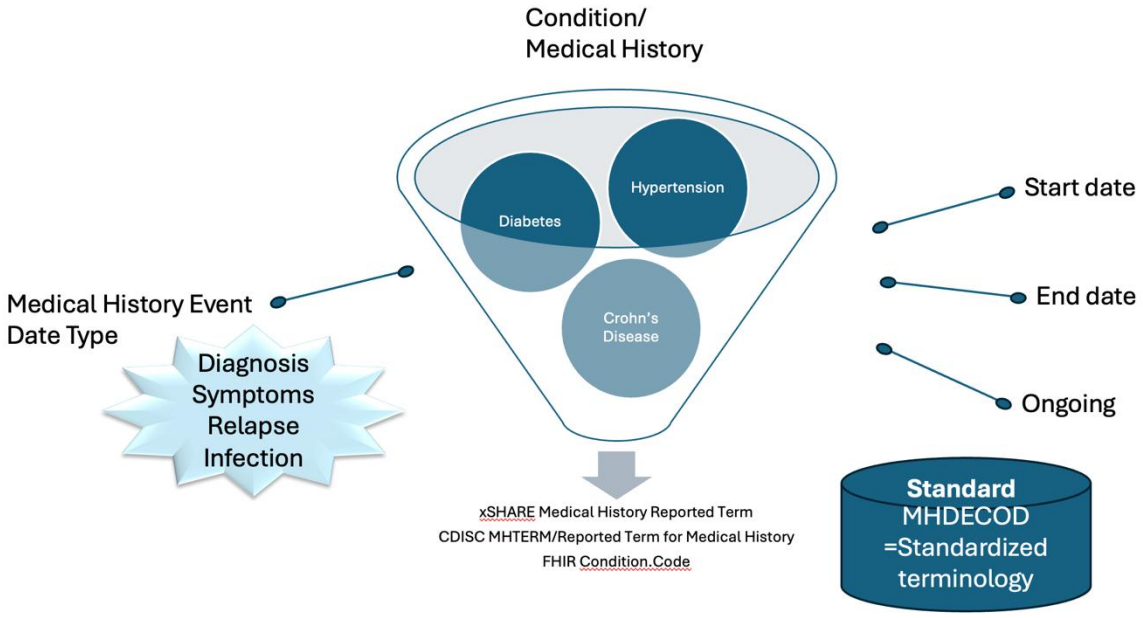

Figure 8: Diagrammatic representation of the terminology and model concepts to represent

5 The IPS+ technical specification

The overarching scope of the xShare IPS+ FHIR Implementation Guide is to provide implementers with additional support for leveraging the HL7 IPS and the supporting documents available within this IG for clinical research and population health. It further builds on the HL7 International Patient Summary Implementation Guide (https://hl7.org/fhir/uv/ips/index.html). Although the IPS dataset is a "minimal, non-exhaustive set of data elements required for the international patient summary", it forms a good basis for use in research and public health. In order to be of use there, a number of recommended and optional categories will be considered as required.

The role of the core harmonized terminology, valuesets and codelist alignment, and the model-to-model mapping included in this scope –FHIR to CDISC mapping of IPS profiles, data element item to item map.

The content available for download includes the xShare Core Harmonised Data Elements, the IPS FHIR to CDISC SDTM Mapping Specifications for the HL7 IPS v1.1.0 to CDISC SDTMIG v3.4 for the following profiles: Patient, Condition, Medication, Medication Request, Medication Statement, Observation Results Laboratory (includes Observation Results), Procedures, Diagnostic Report, and the base R4 FHIR (release 4 FHIR) resource Encounter; and xShare routine laboratory data items, microbiology data items (with SNOMED codes and CDISC C-codes), a subset of the CDISC LOINC-to-LB (laboratory) mapping, and an analysis of the IPS FHIR valuesets to CDISC terminology codelists.

These tools are envisioned to aid in providing semantic interoperability across the FHIR data model with supporting terminologies and the CDISC SDTM data model including the CDISC terminology curated by the NIH NCI EVS Terminology services.

The harmonized terminology, valuesets and codelists can be downloaded and used by implementers or end users to create a standardized database for IPS+ data. Such database can either be integrated in the implementers' compatible system or used for data mapping through APIs/Queries as detailed in (refer to table below on FHIR queries)

The list of specific IPS+ data elements that are specific for the business use cases, are represented in the annex II of "Analysis of business use cases for use of European EHRxF HIDs in clinical research"

5.1 Downloads

- Proposal for a harmonized core data set across health care, population health and clinical research
- Analysis of business use cases for use of European EHRxF HIDs in clinical research
- Proposed interoperability specification for an International Patient Summary for Research mapped to international standards
- xShare Core Harmonised Data Element Set
- Valuesets-Codelists in Support of xShare Core
- FHIR to CDISC Mapping Documents

5.2 Artifacts Summary

Table 1 provides other useful implementation guides across the standards ecosystem that inform secondary use of health data for clinical research and population health.

Table 1: Resources for research and secondary use of data

Source	Link
HL7 Vulcan Adverse Event Clinical Research v1.0.1	https://hl7.org/fhir/uv/ae-research-ig/
HL7 Vulcan Adverse Event Clinical Research R4 Backport v1.0.1	https://hl7.org/fhir/uv/ae-research-backport-ig/
HL7 Vulcan Retrieval of Real World Data for Clinical Research v1.0.0	https://hl7.org/fhir/uv/vulcan-rwd/
HL7 Vulcan Clinical Study Schedule of Activities v1.0.0	https://hl7.org/fhir/uv/vulcan-schedule/
FHIR to CDISC Joint Mapping Implementation Guide v1.0.0	http://hl7.org/fhir/uv/cdisc-mapping/STU1/
CDISC/TransCelerate Digital Data Flow and The Unified Study Definitions Model	https://www.cdisc.org/ddf
CDISC Study Data Tabulation Model v2.0 & Study Data Tabulation Model Implementation Guide (SDTMIG) v3.4	https://www.cdisc.org/standards/foundational/sdtmig
CDISC Clinical Data Acquisition Standards Harmonization Implementation Guides (CDASHIGs) v2.3 (and CDASH Model v1.3) Includes Case Report Form examples	https://www.cdisc.org/standards/foundational/cdash
CDISC CDASH Serious Adverse Event (SAE) Supplement v2.0	https://www.cdisc.org/standards/foundational/cdash/cdash-sae-supplement-v2-0
CDISC Controlled Terminology (also available in the CDISC Library through the API)	https://www.cdisc.org/standards/terminology/controlled-terminology
CDISC Therapeutic Area by Disease (includes example CRFs and data tables—CDASH, SDTM, ADaM)	https://www.cdisc.org/standards/therapeutic-areas/disease-area
CDISC SDTM and SDTMIG Conformance Rules v2.0	https://www.cdisc.org/standards/foundational/sdtmig/sdtm-and-sdtmig-conformance-rules-v2-0
Pinnacle21 (Conformance Rule tool)	https://www.pinnacle21.com/about
NIH NCI EVS Thesaurus Browser (source for Data Element Concepts)	https://evsexplore.semantics.cancer.gov/evsexplore/welcome
CDISC eCRF Portal, Examples Collection and Articles, includes RedCap link with CDASH forms	https://www.cdisc.org/kb https://www.cdisc.org/kb/ecrf
CDISC Library uses linked data and a REST API to deliver CDISC standards metadata to software applications that automate standards-based processes.	https://www.cdisc.org/cdisc-library

CDISC Data Exchange Standards	https://www.cdisc.org/standards/data-exchange
IHE International Quality, Research and Public Health includes integration profiles: • Retrieve Form for data capture (RFD) • Retrieve protocol for execution (RPE)	https://www.ihe.net/ihe_domains/quality_research_and_public_health/
Biomedical Research Integrated Domain Group (BRIDG)	https://bridgmodel.nci.nih.gov/ https://www.iso.org/standard/83433.html
Clinical Research Sponsor Laboratory Semantics in FHIR Implementation Guide	https://hl7.org/fhir/uv/cdisc-lab/
OHDSI Clinical Trials Working Group (draft maps from SDTM to OMOP)	https://github.com/OHDSI/ClinicalTrialsWGETL/wiki
SNOMED-CT – LOINC browser	https://loincsnomed.org/

Additional resources that may be helpful, however, were not specifically designed targeting secondary uses of data are in Table 2.

Table 2: FHIR Resources

EU Public Health Electronic cross-border health services	https://health.ec.europa.eu/ehealth-digital-health-and-care/electronic-cross-border-health-services_en
FHIR Registry of IGs	https://fhir.org/guides/registry/
EU FHIR Extensions	https://hl7.eu/fhir/extensions/
EU Laboratory FHIR IG	https://hl7.eu/fhir/laboratory/
Provenance guidance	https://hl7.org/fhir/us/davinci-cdex/task-based-approach.html#provenance

Table 3 provides links to resources for query of data elements to facilitate the protocol feasibility use case. Further resources may be added later, through engagement with early adopters of this specification.

Table 3: Example Resources for FHIR and Queries

Source	**Link**
Mobile access to Health Documents (MHD), v4.2.2 - Trial-Implementation	https://profiles.ihe.net/ITI/MHD/
Using CQL with FHIR, v1.0.0 - STU1	https://hl7.org/fhir/uv/cql/STU1/

6 IPS+ adoption within the use cases

This section outlines how the IPS+ specification could be incorporated within the use cases presented earlier. The work flow of each use case is described, including the role of the IPS+. It is assumed that the IPS+ data is either held in regional or national repositories, or is retrieved on a patient specific basis by the patient using the xShare yellow button. In practice other IPS+ data flows might be implemented.

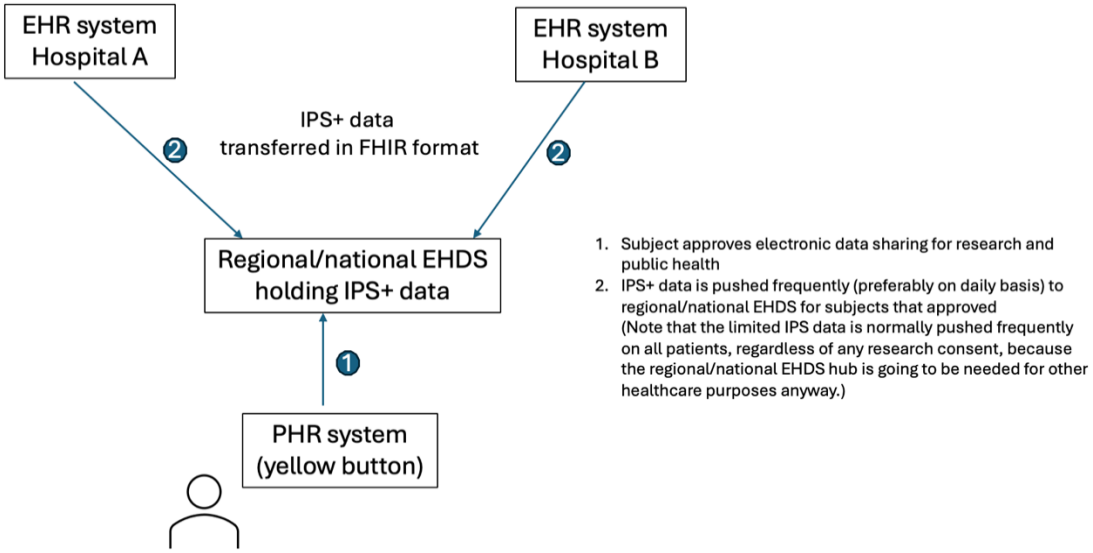

Figure 9: Simplified flow for the base steps of the use cases

6.1 Use Case 1 – Study Feasibility

The capability to utilise the IPS+ in Use Case 1 relies upon a sequence of adoption and implementation decisions within a country, summarised as workflow steps below, from D5.2.

1. The IPS+ is endorsed by Member States and the EC, and included within the published European EHRxF.
2. EHR system vendors implement and upgrade their deployment sites with IPS+ export interfaces (APIs) to relevant regional or national platforms, and include user interface and data entry workflow support to optimize the completeness and quality of IPS+ data elements (e.g. a prompt to add a new diagnosis to the summary)
3. Regional and national health systems establish population repositories of European EHRxF data, along with processes to maintain its currency from different healthcare provider systems. These will be health system repositories established mainly for patient care delivery purposes, populated through identifiable data exports from healthcare provider EHR systems, as many countries already do. The data controller of these repositories is normally the regional or national health system (e.g. the health ministry).
4. Regional and national health systems design and implement data reconciliation methods to align the correctness of the IPS+ data held centrally, when there are inconsistencies in the data values for the same patient across different healthcare provider exports.

5. Regional and national healthcare systems and data protection officers set policies, agreements and contracts to enable the reuse of these repositories for clinical research, including patient awareness and education.
6. Companies making clinical research platforms implement federated query channels to these new repositories and update query tools for protocol designers study feasibility analysts.
7. Pharma and MedTech companies train relevant staff and adapt their workflows to leverage EHR data for clinical trial design and recruitment scenarios.

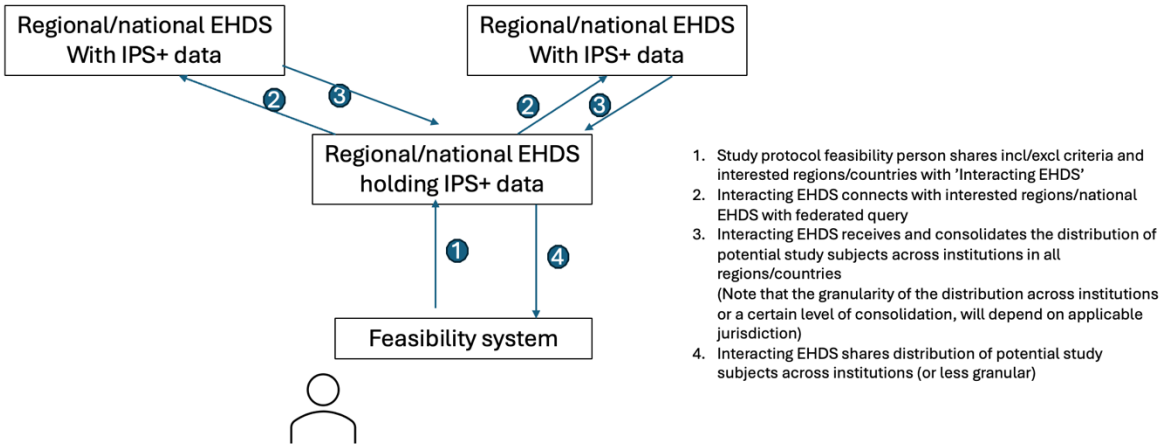

Figure 10: Simplified flow for use case 1

6.2 Use Case 2 – Individuals share data for potential study participation

In Use Case 2, data sharing for individuals requires the existence of a PHR app connected to national/regional infrastructure. Health data needed for the pre-screening tool must be available in the IPS+ and able to be exchanged through an interoperability system, the xShare Yellow Button. IPS+ data and national/regional infrastructure's data are standardized and mapped between the IPS and clinical trial system using the standardized value-sets and code-lists available to download in part 5 of this document. It pre-exists in a database either integrated to the pre-screening tool or accessible to recognized third parties through API calls.

Patients/healthy volunteers have access to a PHR app to access their health data and using this app they can assess their eligibility for a clinical trial. They are interested and want to know if they can be included in a clinical trial, in one of the hospitals near to their home.

PHR and participant workflow steps, from D5.2

1. The user accesses to the PHR app, (The data format is European EHRxF/xShare core data element set)
2. The user triggers (and gives consent for) the sharing of their data after clicking the xShare Button (toggle button)
3. The health data is shared with the pre-screening application and mapped with pre-screening questions "pre-screening questions available to the participant"

4. The pre-screening application interprets the data through a questionnaire filtering the potentially compatible clinical trial
5. The results of compatible studies and participating centres are accessible to the patient, including a percentage of compatibility. These features are beyond the scope of this use case.
6. The user can choose a study, several studies if applicable, and the hospital of their choice and gives consent for their data sharing to the chosen centre.
7. The user gives consent for their data sharing (access to the IPS+) by the chosen centre.
8. The centre receives a notification with the results and can access data to contact the patient/healthy volunteer to plan an on-site visit and assess the patient/healthy volunteer's full eligibility.
9. The centre accesses the user's pre-screening data.
10. The centre contacts the user to schedule the on-site visit and prevents the user coming in when there is limitation in their ability to participate in the study. This reduces the number of unnecessary visits and invasive examinations.
11. The user full eligibility is assessed by the site during the onsite visit.

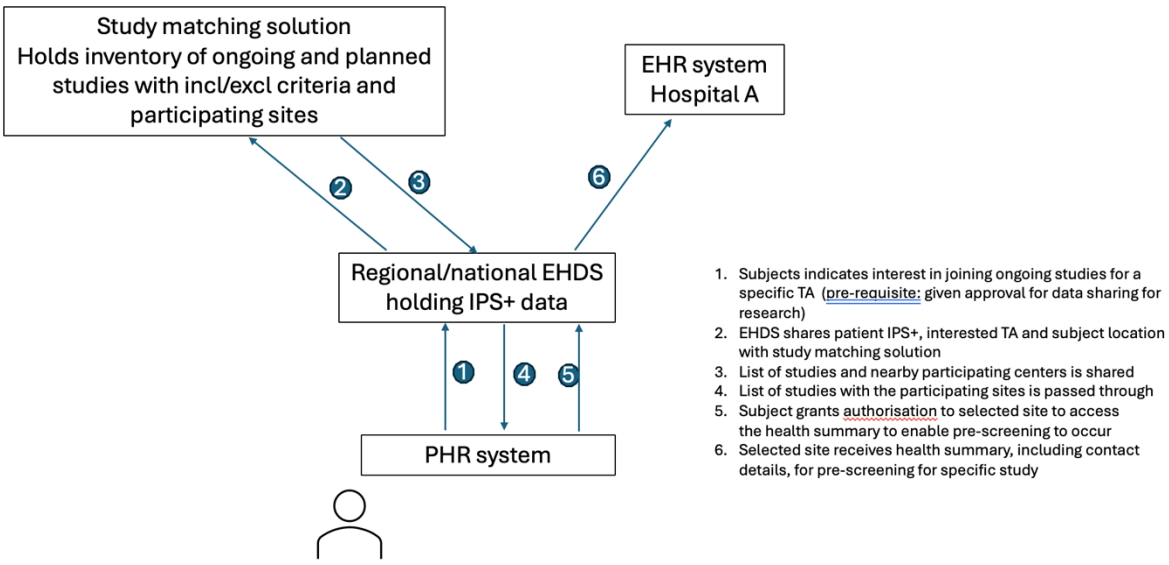

Figure 11: Simplified flow for use case 2

6.3 Use Case 3 – Study support PHR/EHRs to Study Database Systems or EDC

The consenting patient enrolled in the study is included by the investigative team of the centre. The Study allows eCRF automatic filling from existing health data. The patient has access to their PHR app containing a section allowing IPS+ data sharing for clinical research. The patient agrees to the automatic health data filling the eCRF in the context of this study.

1. Approval of the study and the site by the respective/reference regulatory bodies in each country where the CT is ongoing.

2. Clinical study protocol data elements are mapped with source IPS+ items, by the investigator systems (EHR) or centrally for the (multi-site) trial by data manager/EHR vendor/data source manager etc.
3. Patient is identified as candidate by the centre and is enrolled in a retrospective or prospective study. The patient signs the study ICF and data sharing permission only for the concerned study. Consent is obtained in a GDPR compliant manner.
4. The Study allows eCRF automatic filling from existing health data and the patient have access to their PHR app, containing a section allowing data sharing for clinical research.
5. The patient agrees with the automatic health data filling the eCRF in the context of this study.
6. The patient has access to a PHR App with the xShare Yellow Button. This enables the patient to download their European EHRxF data and to forward this to the study centre (or to provide an authorisation to the IPS+ data source to send it to the nominated trial centre directly). The Study team assists the patient to link their inclusion number to the study in the PHR App when forwarding the data or authorising access.
7. Health data from their IPS+ is mapped to the corresponding data in the eCRF.
8. The investigation team completes the collection of additional data not in the IPS+, according to the study eCRF, and performs a manual or automatic quality control on the data collected.
9. Data is managed in a controlled and protected environment.

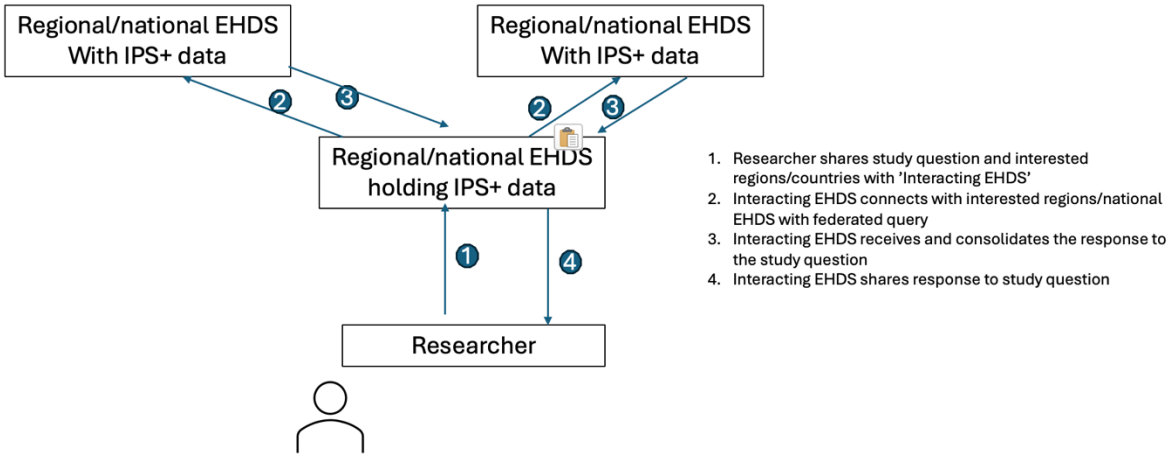

Figure 12: Simplified flow for RWE research

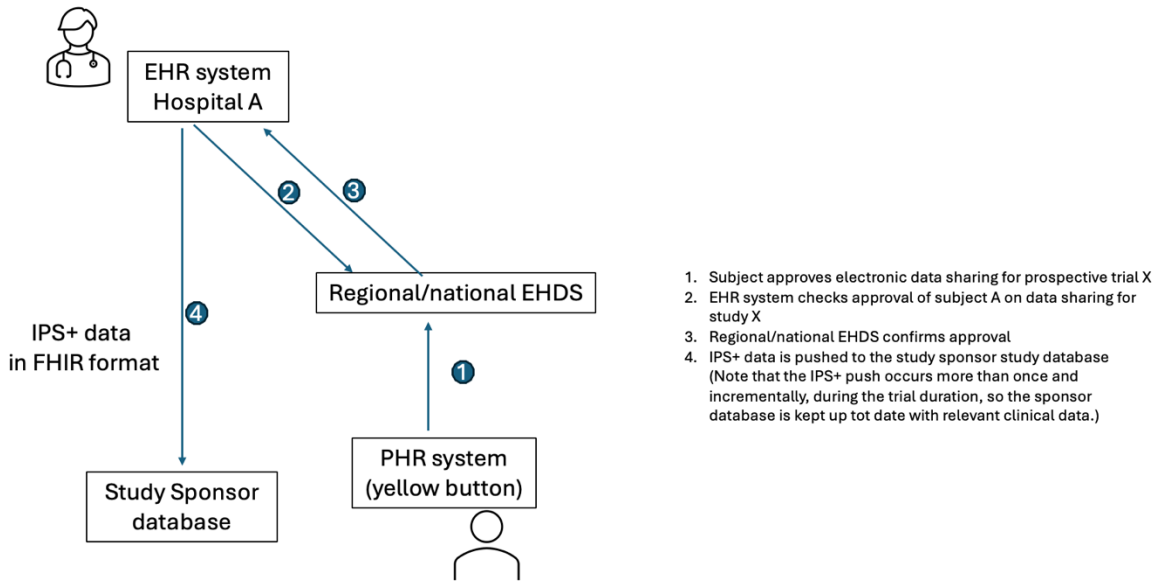

Figure 13: Simplified flow in view of prospective trials

It should be noted that the clinical study protocol is likely to contain data elements beyond those defined in the IPS+. The data from the IPS+ will therefore not result in the entire filling of the eCRF. This workflow therefore provides only part of the study dataset, but is considered valuable because these are frequently copied across from the patient's health record.

If, for example, an examination or visit unrelated to the study occurs while a patient is participating and results for example in an update to the patient's medication list, or in an adverse event, the updated IPS+ can be sent to the study centre and data updated in the eCRF.

If a patient changes their mind and no longer wishes their IPS+ data to be used in the study, they can cease forwarding downloads or cancel their authorisation. (Because clinical trial data needs to be retained long-term as evidence of the trial centre and sponsor duty of care, historically transfer data will not normally be deleted.)

6.4 GDPR compliance and information security

The xShare Yellow Button utilises an enhanced data subject right under the GDPR, by enabling a patient to access a complete copy of their European EHRxF data in a computable standardised form, utilising the same standards that are used to exchange this information between healthcare systems. The IPS+ is proposed as the representation of this content.

The EHDS Regulation permits an individual to forward their exchange format information to any other parties, for example to obtain a second clinical opinion or to participate in research. The trial centre should publish its data protection policy and notices, so that the patient is well aware of the GDPR-compliant terms and safeguards that will be applied to any data they provide to the trial centre they have chosen. The act of forwarding the information effectively provides their informed consent for the recipient to legally hold their personal European EHRxF data according to those published terms and safeguards.

If the patient passes pre-screening, screening, and then becomes enrolled in the clinical study, the trial centre and sponsor will then need to retain their copies of the patient's health information on a long-

term basis, as their record of having performed a duty of care to the patient. This is usually the GDPR legal basis of legitimate interest in industry clinical studies. This is why, if a patient withdraws from a clinical study, their historic data will not be deleted. It will be a matter for the trial centre, in its published notices, to make clear what right of deletion a patient may exercise at the pre-screening stage when no duty of care has yet been provided.

The xShare Yellow Button workflows additionally need to be secure, normally to the information security standards that the national health system would utilise for its own communications between healthcare providers or between a healthcare provider and a patient. Since this representation will utilise HL7 FHIR, it is possible that its information security and access control standards will be used:

- http://hl7.org/fhir/security.html
- https://build.fhir.org/secpriv-module.html

The information security measures needed for the data flows that utilise the IPS+ specification are beyond the scope of this deliverable.

6.5 Data quality

The EHDS Regulation places and obligation on EHR systems to document the consistency, accuracy and completeness of data within the scope of the European EHRxF. It is not clear from the Regulation how this quality information is to be handled, provided or communicated whenever an extract is generated and communicated. This differs from the data quality and utility label to be applied to datasets for secondary use, when the (optional) label is to be included within the data set catalogue.

The EHDS Regulation sets no minimum data quality standard for primary use (but only that it is documented by EHR vendors) and makes no provision for any efforts that should be undertaken by Member States, health systems or EHR vendors to assure good data quality or to improve poor data quality. This means that the IPS+ data will be obtained “as is”. If the clinical research use cases have minimum data quality standards, for example before data is transferred into a study database, then these data quality assessments need to be undertaken by the party orchestrating the data transfer.

7 Future plans

The specification provided in this deliverable is an initial version, developed by experts in these different standards. It is intended to be used during 2025 by several demonstrators that will seek to implement and test data flows and data transformations corresponding to one of the use cases in D5.2, or potentially to another similar use case. A second version of this deliverable specification will be published in the winter 2025-26 as an update, benefiting from the experience of those implementers.

It is intended for the final technical specification to be offered as a proposal for adoption by the European Commission as part of its overall specification of the European EHRxF.