xShare

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

WP5
D5.2 v. 2024-08-30 Analysis of business use cases for use of EHRxF HIDs in clinical research – WP5.1-TTSA
Date: 30.08.2024

Project title:	xShare - Expanding the European EHRxF to share and effectively use health data within the EHDS.
Grant Agreement:	101136734
Call identifier:	HORIZON-HLTH-2023-IND-06-02
Dissemination level:	Public or Confidential, only for members of the consortium and the Commission Services

This project has received funding from the European Health and Digital Executive Agency (HADEA) under grant agreement no. 101136734.

Deliverable description

Number and name of deliverable:

Publishable summary: eliverable D5.2 is an analysis of business use cases (BUCs) for the use of the EEHRxF and xShare Yellow Button in clinical research. It examined methodologies and workflows where real-world data (RWD) is valuable. The need for automated, harmonized data sharing via EEHRxF was emphasized. Three BUCs were identified: study feasibility, patient pre-screening, and study support. Study feasibility used EEHRxF for federated health data queries, aiding protocol design and site selection. The patient pre-screening use case empowered patients to control and share their data for clinical trial eligibility, addressing recruitment challenges. Study support involved efficient data sharing between patient health data and case report forms (CRFs). Overall, Deliverable D5.2 demonstrated the significant value of EEHRxF and the xShare Yellow Button in clinical researchpromoting efficiency, individual empowerment, and data-driven insights.

Status:	Draft
Version:	1.3
Last update:	30.08.2024
Deadline:	31.08.2024
Actual delivery:	02.09.2024
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Statement of originality

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Change History

Version	Date	Author	Organization	Description
0.1	31.07.2024	Charlotte Cameli, Norman Sabbah	TTSA	First draft
0.2	07.08.2024	Stefano Dalmani Dipak Karla Rebecca Baker Rhonda Facile Rebecca Kush Carola Schulz Sofia Franconi	FTGM i-HD CDISC CDISC CDISC Empirica IHE (And early internal reviewer)	Working group 5.1 review of the first draft: Wording review, Executive summary, Edition review
1.0	09.08.2024	Charlotte Cameli	TTSA	First final version for internal review
1.1	19.08.2024	Charlotte cameli	TTSA	Internal review
1.2	28.08.2024	Charlotte Cameli Mie Hjorth Matthiesen	TTAS MedCom	Final internal review
1.3	30.08.2024	Catherine Chronaki	HL7 Europe	Final Review

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List of abbreviations

Please refer to the i~HD Glossary: https://glossary.ramit.be/public/index.cfm

Abbreviation	Term
AE	Adverse Event
BUC	Business Use Case
CDA	HL7 Clinical Document Architecture
CRF	Case Report form
CRA	Clinical Research associate
CRO	Clinical Research Organization
CT	Clinical Trial
EC	European commission
eCRF	Electronic Case Report form
EHDS	European Health Data Space
EHR	Electronic Health Record
EMR	Electronic Medical Record
EEHRxF	European Electronic Health record Exchange Format
FHIR	HL7 Fast Healthcare Interoperability Resources
HCP	Healthcare Professional
HID	Health Information Domain
ICF	Informed Consent Form
ICT	Information and Communication Technology
IPS	International Patient Summary
RWD	Real World Data
PHR	Personal Health record
RCT	Randomized controlled trial
RWD	Real World Data
S-EHR	Smart-EHR
SAE	Serious Adverse Event
SIV	Site Initiation Visit
WG	Working Group

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Executive summary

This deliverable aims to define, explore, and analyze various Business Use Cases (BUCs) for the application of the European Electronic Health Record Exchange Format (EEHRxF) and the role of the xShare Yellow Button in clinical research. The work began with an examination of a range of methodologies and workflows where Real-World Data (RWD) has recognized value, drawing on experiences from past EU projects. These projects highlighted the evolution from structured data in Electronic Medical Records (EMRs) to the application of RWD in clinical research. They also demonstrated the need for automation and consistent, harmonized data sharing facilitated by the EEHRxF.

The working group established candidate BUCs, categorized into study feasibility, patient pre-screening, and study support. Exploring study feasibility involved applying the EEHRxF for federated queries on health data repositories. This approach allows Clinical Trial (CT) designers to gather valuable information about patients' active health records and locations, enabling protocol design adaptation and investigative site selection. In the patient pre-screening use case, the xShare Yellow Button acts as a trigger within a Personal Health Record (PHR) application. This feature empowers patients to control their data, allowing them to share it with the purpose of assessing their potential eligibility for clinical trials. By enabling patients to assess their own eligibility, this use case addresses a critical issue in clinical trial operations: patient recruitment. Then, study support is facilitated by data sharing through the EEHRxF, enabled by the xShare Yellow Button in a PHR app. This data sharing allows for generalized mapping between patient health data and the clinical trial Case Report Form (CRF) data. Industrializing this flow saves research teams valuable time and enhances quality and efficiency. Each of these BUCs has demonstrated the benefits of the EEHRxF.

Among the BUCs, special emphasis was placed on the use of mobile devices, as two of three use cases involve a PHR app. This leverages the portability clause of GDPR, empowering patients to control their data. The PHR app, fed by structured patient data from their EHR or other PHR (such as MyHealth@EU), is highly valuable for selecting candidates for clinical research. This is demonstrated in the pre-screening BUC and extends to the automatic feeding of CRF data in clinical trials. Working on the results of Deliverable D5.1, "Proposal for a Harmonized Core Data Set Across Health Care, Population Health, and Clinical Research," helped identify the data sets defined for these use cases and the commonly recurring data items.

This deliverable goes beyond describing BUCs by drafting detailed user stories (US) for each BUC. These US provide guidelines for the initial functionalities related to the xShare Yellow Button, expected in the following task of the Work Package 5, "European EHRxF in Clinical Research: Core Set, and IPS+R." This use case also highlights the interest in these three BUCs and their interconnections by describing the journey of the EEHRxF and the xShare Yellow Button through a clinical trial flow.

Deliverable 5.2 has demonstrated the significant added value of the EEHRxF and the xShare Yellow Button in clinical research by analyzing three different business use cases, promoting efficiency, individual empowerment, and data-driven insights.

1. Introduction

1.1 The objective and structure of this deliverable

The xShare project aims to develop the xShare Yellow Button empowering citizens to share their data at the EEHRxF, with a click-on-a-button. WP5 focuses on the application of the format on clinical research. The aim of task 5.1 is to carry a Business Use Case (BUC) analysis to identify clinical research use cases leveraging Electronic Health Record (EHR) data and investigate the General Data Protection Regulation (GDPR) implications and consent models for providing data to patients in the context of the EHDS regulation.

The rest of chapter 1 summarizes the value of RWD in healthcare, research, the different methodologies related to clinical research and the link with the GDPR portability clause. Chapter 2 presents the methodology adopted for the Business Use Case (BUC) analysis, including the complete listing of the topics suggested, the US method and the choice of the overlap with the International Patient Summary (IPS), i.e. EEHRxF/IPS. Chapter 3 presents each of the 3 selected BUCs and the US related, data of interest from the EEHRxF. Chapter 4 proposes an analysis of each BUC on a larger scale of the deliverable. A bibliography is given in Chapter 5, Appendixes are detailed in chapters 6-7.

1.2 Real World data value

Real-Word Data refers to “data relating to patient health status and/or the delivery of healthcare routinely collected from a variety of source” (Panagiotakos, 2022). Traditional sources of RWD include third-party health insurance claims, EHR, laboratories, disease or products registries, and patient health survey (Simon Dagenais, 2022). EHRs goes beyond Electronic Medical Records (EMR), which are the digital version of the medical record. Indeed, they are built to share a significant source of data by providing demographics, medical history, medication details, allergies, immunization status, radiology images, vital signs, personal statistics (like age and weight), and billing information with all the clinician involved in the patient’s care. Therefore, EHR are real-time, patient-centered records that go beyond standard clinical data collected in a hospital or by a medical caregiver, providing a complete overview of overall medical care (Seidman, 2011). Studies have also shown that structured and standardized EHRs may increase data quality and reuse possibilities but may also increase recording time, which negatively influences adoption and ease of data recording (Cornet, 2019). In addition, patients can access their health data on PHR application, which is a secure, online store of information about a person’s health, care and well-being that is managed by the individual, with information added by both the individual and their healthcare provider: PHR aims to empower patients over their data (Chapman, 2022).

As a consequence, data within EHR systems is of variable quality, and a relevant portion of the data is still being captured in free text and is not directly processable. To solve this issue an identification of critical health data for creating the IPS has been made. While EHRs manage a broader range of patient data, the IPS focuses specifically on essential information needed for the international patient summaries. Indeed, this is a set of standardized data classified from Header to Required, Recommended and Optional. The IPS serves as a bridge between a patient’s “home” health and care

environment and any other clinical settings they may visit, whether within their country or across borders. It involves standard components and customized specifications to ensure seamless operation. Originating from the European eHealth Network, the initial EN 17269 standard defines the purpose and building blocks of the IPS. HL7 offers two implementation approaches for the IPS: Clinical Document Architecture (CDA) and Fast Healthcare Interoperability Resources (FHIR). These enable direct exchange of structured IPS data between EHRs systems. SNOMED International provides the IPS Free Set, allowing consistent coded entries for patient summary sections like allergies, problems, procedures, and immunizations. IHE profiles contribute to support IPS adoption, facilitating functions such as publishing, accessing, and retrieving IPS content. The IPS enhances patient safety by ensuring critical clinical information is readily available during unplanned or emergency care (Anonymous, 2023). The deliverable 5.1 "Proposal for a harmonized core data set across health care, population health and clinical research" reports on an analysis of the IPS data elements not only of greatest research value, but also of population health value and carries out a gap analysis proposing the data elements that could usefully be added to the IPS to maximize its research value and creation of the IPS+R data set. Next, Deliverable D6.1 "Monitoring Framework on National EEHRxF Uptake and EEHRxF Standards Hub Performance" will assess the uptake of the EEHRxF standards on Member State level.

Researchers can use EHR data for clinical studies, leveraging its rich information on patient health and healthcare delivery. However, to be efficient there is a necessity to have a standardized process for data abstraction, when conducting EHR-based clinical studies (Sunyang Fu, 2020). RWD holds great potential for generating real-world evidence (RWE), for designing, conducting clinical trials and answering questions that may not be addressed otherwise. The volume and complexity of a RWD, including EHR, requires innovative data processing and analysis techniques, while maintaining scientific rigor and ethical considerations (Fang Liu, 2022). The research community has a lot of expectations for the use of RWD and the generation of RWE to improve the knowledge about health. There is a number of disparate standards and systems currently in use to support the collection and analysis of RWD (Facile, 2022) and a standardization of RWD would allow a considerable improvement of the field of clinical research. Standardized high quality RWD would accelerate clinical research and, therefore health care through development of new treatments, health care customization, better follow-up on side effects, health care medico-economic analysis, and new medical practice guideline development.

1.3 xShare project's rationale

Before the xShare Project, several projects carried out over the past decade address the problem of how to enhance the use of real word data by the improvement of system, organization interoperability and format standardization. They all contributed, at their own level, in the xShare project's background development. xShare is standing on the shoulders of these projects and they have, in one way or the other, helped shape the project.

It started with the EHR4CR (Electronic Health Records for Clinical Research) project conducted between 2011 and 2016, which aimed to improve efficiency of clinical trials, design in order to respond to the constant and growing major issue of clinical research: the patients recruitment difficulties and clinical trial cost increase. This project's ambition was to design a brand-new European platform, using

a model-driven engineering approach, to host a set of reference clinical terminologies. This project proved that the reuse of EHR offers an opportunity for clinical research.

The Trillium II project was conducted between 2017 and 2019 and aimed to reinforce interoperability between EHRs, focusing on the IPS standards. The IPS is a cross-border, minimal and non-exhaustive set up of clinical data for a patient, allowing building a bridge between the patient's "home" health and care environment, and any other place where the patient needs to consult a healthcare professional. Trillium II aimed to accelerate health innovation and reduce the commercial barriers to interoperability by promoting adoption of the IPS.

Trillium II aimed to build a solid methodology to enhance the EHR patient's health data for research and innovation. Furthermore, the patient's position in this process should be central, and in this objective, the project InteropEHRate was conducted between 2019 and 2022 and aimed to enable citizens to share their data with research centers from their own smartphones with Smart-EHR (S-EHR). This project contributed to the EHR interoperability by a patient-centric approach.

The development of EHR interoperability leads to the question of the different formats for data sharing, and the need to develop a workable, interoperable and secure cross-border format. In 2019, the European Union supported projects to facilitate cross-border sharing of health data. The goal is to support new use cases, such as laboratory results, medical imaging and hospital discharge report, while involving policy actors and stakeholders. EHR interoperability improves healthcare delivery by ensuring that the right data is available at the right time, to the right person. The project X-eHealth (2020-2022) worked on further developing the EEHRxF through the standardization and the harmonization of health data to a European level. The ongoing project XpanDH (2023-2024) aims to build the capacity of individuals and organizations to create, adapt and explore the use of interoperable digital health solutions through shared adoption of EEHRxF across the EU.

EHRs serve as crucial sources of patient information. Recognizing their value, researchers increasingly leverage EHR data for clinical trial design, optimizing eligibility criteria, identifying suitable patient numbers, and streamlining recruitment. Interest also grows in using EHR data to create virtual (synthetic) patient cohort, enhancing recruitment and enabling observational studies. However, challenges include missing data, bias, variability, and semantic heterogeneity. Despite these obstacles, RWD is gaining consensus for safety and efficacy assessments in drug approvals. Randomized controlled trials (RCTs) have limitations, making EHR data's reuse essential for efficient, equitable clinical research across diverse populations and healthcare sites. The next step for the project xShare is to contribute to the expansion of the EEHRxF, in order to enable citizen to safely share their health data with a click-on the xShare Yellow Button. This project will need citizen engagement, a crucial part to explore health data, which will truly realize the vision of the European Health Data Space (EHDS) highlighting the fact that EEHRxF offers various possibilities for secondary use, and application to clinical research.

This deliverable 5.2 will explore a range of applications for the EEHRxF to demonstrate its relevance for clinical research applications.

1.4 Clinical research methodologies

Clinical research and medical care are closely related activities (Sacristán, 2015), representing two sides of the same angle. While patient care involves providing treatment and managing health conditions, research aims to generate knowledge that can improve patient outcomes. It is a leverage of efficiency for healthcare establishments and outpatient medicine, in terms of attractiveness, medical demography and early dissemination of innovation to all patients.

Setting up a clinical trial involves many stakeholders:

- Sponsor: The sponsor is the entity behind the project and its funding. It can be an industry (pharmaceutical company, medical devices producer, etc.), an academic structure or a research center. The project can be delegated to a clinical research organization (CRO).
- Investigation sites: The investigative site are the centers where the patients are being included and followed. It is commonly a hospital or healthcare structure, but it can also be specific research sites. The professionals working at Investigation site for a clinical trial compose the investigative team. This team is composed of the clinical investigator and associated professionals (Clinical research associate, Clinical research nurse, Clinical research technician, etc.)
- IT providers: There is a lot of digital tools developed to conduct the research. One of the most important tools is the electronic Case Report from (eCRF), which provides the forms for the database of all the data collected for the need of a clinical trial, and analysis at the end of the study.

Clinical research methodology is a very precise process following the same big steps: design, operation and analysis. The first step to conduct a clinical trial is to develop the study protocol, this document describes all the processes, objectives and tools of the study. The first question to create a new study protocol is to consider the purpose of the study. Then, the study methodology should align with the purpose e.g. non-interventional real-world studies, comparative studies (randomized, before/after, cross-over), retrospective/prospective studies, and single-center/multi-center studies. The primary outcome criteria, which is the parameter measured to highlight the result of an event or intervention and should match the study purpose, objectives and the financial aspects, material resources. The protocol must be designed taking into consideration its feasibility in the field and verifying if recruitment's objectives, based on patient's eligibility criteria and the sample size, are achievable within the specified time frame. A recruitment goal will be defined with each investigative site's principal investigators of the different investigative sites.

1.5 EEHRxF's potential contribution to Clinical Research

The EEHRxF application can benefit from clinical research at multiple levels, including protocol feasibility assessment, site selection, patient pre-screening prior to invitation, consent management, data transfer after consent, core eCRF completion, and innovative trial design. In this deliverable, we will focus on three major topics:

- Study feasibility,
- Patient pre-screening
- Study support.

The following paragraph provides further details on the relevance of these topics within the scope of clinical research.

Study feasibility is one of the most crucial steps, if not the most crucial one, to ensure smooth running of the clinical trial and quality results. Study feasibility must consider whether the research is feasible in terms of objectives and methodology. This involves considering available resources (financial, material, human) and potential constraints. As patient recruitment is one of the most challenging parts of a clinical trial (Raisa B Gul, 2009), making sure during the study feasibility that a sufficient number of patients can be included, is a very important part. To do this, the trial manager needs to make sure that the investigation site participating in the clinical trial has a sufficient number of patients candidates in their active file. Moreover, the patients' characteristics population defined by the protocol with the eligibility criteria, must match existing patients. Therefore, the protocol feasibility assessment is directly linked with the site selection. There are two ways to ensure having the right number of patients, the first one is to select enough sites to achieve the recruitment goals, and the other one is having a fixed number of sites and selecting the ones which will have the recruitment capacity to achieve the goals. The number of investigation sites have a substantial impact on the cost of the clinical trial, and the challenge is to get the good sites to limit the number of centers, while still including the right number of patients. Getting information on patients followed in the different sites by EHR data is a very robust way to evaluate the potential of inclusion of the sites.

Once the clinical trial documentation has been written and the sites chosen, the sponsor/CRO is in charge of obtaining the regulatory approvals to conduct the study. The regulation may differ from one country to another but, at the European level, there is a desire to comply with the European regulation (n°536/2014, n°2017/746, n°2017/745).

Once the clinical trial receives all the approvals, the study can start in the investigative sites, after a training of the investigative team for the study, during the Site Initiation Visit (SIV). Sites receive the approval to enroll and now have to select patients compatible with the study.

To do that, patients must match all the inclusion criteria and have none of the exclusion criteria. In order to select the potentially eligible patients, the research team accesses the active EHR file to contact the corresponding patient. The first proposal to participate can also be made during a medical consultation. This selection phase, before the informed consent form signature (ICF), is called pre-screening. It is the first step of a patient's eligibility assessment, done with the health data of routine practice. This step is crucial, as a precise and effective pre-screening allows the investigative team to save significant time in the recruitment process. Structured data from EHR is a very good pool of data to evaluate the potential eligibility of a patient. The EHR data sharing through the xShare Button, for pre-screening at the patient's initiative, with pre-screening tools (e.g. pre-eligibility questionnaires) on the market would be a real time saver for the research teams. However, in most of the cases, to complete the patient inclusion, a screening phase validation of all eligibility criteria will be performed after the ICF signature, as it is out of the routine practice.

The ICF signature is the most important ethical prerequisite. No research specific act, no data collection or transfer, can be done without patient consent. Once the patient agrees to participate in a clinical trial, the machinery gets underway, and the data collection can start in parallel with the patient's follow-up. Most of the data collected for clinical trial is entered manually, by the research team, from the medical records to the eCRF, which will constitute the data analysis set for the trial. This database is mainly composed of forms and structured data. eCRF filling is one of the biggest time-consuming parts of the clinical trial for the research team. Automatization of this process, thanks to the secure data sharing with the xShare Button, would be a major improvement, allowing the team to focus on patients' follow-up, while maintaining the full control of data transmission in patients' hands.

It is the responsibility of the sponsor to ensure the clinical trial monitoring and data accuracy. Quality control (or monitoring) in clinical research involves verifying the accuracy and completeness of data transmitted from investigative centers to the study sponsor. Its purpose is to ensure the reliability of study results. Typically, quality control occurs at the center where the patient is being followed, under the supervision of the investigating team. A Clinical Research Associate (CRA) may review source documents (such as medical records and laboratory reports) on behalf of the sponsor, comparing them to the data recorded in the investigator's eCRF. Each data filled in the eCRF must be present in the EHR or in the specific documentation of a clinical trial. The automatization of eCRF filling would reduce the human error, human resources assigned and accelerate the CT quality control.

At the end of the CT, once all the patients are recruited and have ended their follow-ups, once all the data have been monitored and after a quality data review with the scientific committee, the data is frozen and can be analyzed leading to the study result.

1.6 European Health Data Space and portability rights

The European Health Data Space (EHDS) is a significant initiative within the European Health Union. It represents the first common EU data space focused on health data, arising from the European strategy for data. Key points about the EHDS include:

Primary Use of Data:

- Empowering individuals to control their health data.
- Facilitating data exchange for healthcare delivery across the EU.

Secondary Use of Data:

- Establishing a consistent, trustworthy system for reusing health data in research, innovation, policy-making, and regulatory activities.

The EHDS ensures secure access and processing of health data. It builds upon existing frameworks like the General Data Protection Regulation (GDPR), Data Governance Act, Data Act, and Network and Information Systems Directive. Member States can offer opt-out options for both primary and secondary use, balancing patient preferences with public interest. In summary, the EHDS aims to

leverage health data for the benefit of patients, researchers, innovators, and regulators while maintaining trust and privacy.

The right to data portability is one of the fundamental rights enforced by the GDPR (Art 20). It assumes that Individuals have the right to receive the personal data concerning them, which they've provided to a data controller, in a structured, commonly used, and machine-readable format. They can then transmit this data to another controller, without hindrance from the original one. The purpose is that data subjects can either store this data for personal use or transfer it to another data controller. To do that, the processing must be based on consent, or a contract and the processing must be carried out automatically. GDPR allows patient to exercise portability rights and the position of the patient regarding their health data into xShare project leverages the need of patient empowerment.

The xShare Yellow Button, when applied to clinical research, enables individuals to exercise directly their data portability rights under the GDPR. By clicking this Button, people can safely download and share their health data. This citizen empowerment regarding data will drive the exploration of health data and contribute to realizing the vision of the EHDS.

Figure 1 presents the template used to work methodically on each BUC of interest. The codes in the first column refers to the different topics of work of this WP5.1 and are defined as follow:

1 - *Specified Theme/objective: Explore protocol feasibility assessment, site selection, patient pre-screening before invitation to participate, consent management, transfer of data after consent, fill core eCRFs, and innovative trial design including a special emphasis on the usage of mobile devices.*

2 - Desk research: State of art of previous and ongoing projects such as RWD research (done by CDISC and partners), EU projects (InteropEHRate, EHR4CR, etc.) and will include an overview of the tools available on the market or to be.

3 - Impact analysis: Evaluate the impact on the efficiency of clinical research, control of individuals over the use of their data and any other relevant conditions including benefits (efficiency, accessibility…) and risks evaluation.

Each business use case should align with the main aspects of the three different topics, but it does not need to address every detail within them. However, collectively, all the business use cases must cover the key items of interest.

Code	Title	<business use case title>	
1	**Business Goals**	<what overarching goals you aim to achieve by its execution?	
1	**Purpose**	<describe the main functionality of the use case – what is it, what does it do? >	
1	**Motivation**	<why is the xShare button interesting in the scope of this use case?>	
1	**Target Group**	<the main beneficiary of the use case (e.g. patients with a specific condition, healthcare provider, etc)>	
1-2	**Stakeholders**	<other entities involved in the use case, that may affect it and/or interact with it (e.g. patients and their representatives, healthcare providers, regulatory bodies, SDOs, IT vendors, etc)>	
1-2	**HIDs**	<the HIDs of the use case. For the xShare project, the following HIDs have been considered: > Patient summary | Electronic prescription | Electronic dispensation | Medical image and image report | Laboratory result | Discharge report | Telemonitoring (new) | Care plan (new) | Other *eHealth tourism and private-public are not HIDs	
1-2	**Scale**	<organizational dimensions of the Use Case: > Cross-border | National | Regional | Intra-organisational | Other	
1-2	**Use Case Objectives**	<the objectives of the use case (e.g. share data on a specific medical condition)>	
2	**Benefits and KPIs**	<what specific benefits do you foresee as a result from its execution? Can you include quantifiable metrics?>	
1-2	**AS-IS (before xShare)**	<How is the use case currently executed ? does it exist?>	
2	**TO-BE (with xShare)**	<how do you envisage to do the process using xShare?>	
	Description	<description of what will do to move from the AS-IS to the TO-BE (e.g. what kind of technology will be used, what kind of interventions, etc.)	
	Actors/Users and their Roles	**Actor** < individuals, external systems, or other software components that play a role in the use case. (e.g. patients and their representatives, healthcare providers, EHR systems, apps and portals, etc.)>	**Role** <Role played>
3	**Use Case Major Challenges**	<Which difficulties do you foresee? Are there any mitigation measures/work arounds?>	
2	**Preconditions**	<conditions and factors that need to be present for the use case to be applied (they could be of diverse nature)>	
2	**Trigger**	<the criteria for the execution of the use case>	
	Flow	<a step-by-step description that indicates the actions that are executed by each Actor to cover the full storyline. May be supported by illustrations, links, schemas, etc.>	
3	**Post conditions**	<conditions that need to be present when the use case is executed (i.e. the outcome of the use case)>	

Figure 1 : BUC template as a basis of work

A list of 10 BUC has been suggested by the working group. The 10 BUCs are presented in more detail in Appendix I: BUC global listing.

The working group conducted a vote to prioritize the BUCs for analysis, within the scope of this deliverable. The goal was to identify the three most relevant BUCs to focus on. This decision was driven by the need to manage study feasibility constraints and avoid thematic overlaps among some BUCs. As a result, it was determined that not all themes would be explored in depth. Instead, the analysis will concentrate on the most pertinent BUCs to ensure a thorough and manageable examination.

1.7 User stories

User stories and use cases complement each other. While use cases depict how users interact with a system, user stories describe features from the user's perspective. As a result, user stories are much shorter than use cases, typically consisting of brief descriptions which teams use as a jumping-off point in development. User stories play a crucial role in Agile development. They validate the alignment between user needs and proposed solutions or use cases. By expressing requirements through concise, straightforward narratives, user stories ensure that the developed functionality meets user expectations. Additionally, they enhance understanding of business use cases. Considering all user needs helps create a comprehensive set of features for different use cases.

In this deliverable, we define different user stories related to each of the three use cases studied. This work will ensure that the BUC has the functionalities required by the users.

Typically, a user story contains three main elements:

- AS A: The user description, which describes who the user is and what his need or wish is.
- I WANT TO: The desired action, which explains what the user wants to do, or what he wants the system to do for him.
- SO THAT: The expected benefit, which describes what the user hopes to achieve by performing the desired action.

The user stories suggested have been classified by relevance level:

- Critical: The functionality associated is to be implemented for the first developments
- Important: The functionality must be taken into account, after the critical ones are being developed
- Not so important: The functionality can be implemented after the critical and important ones.

1.8 Core Data Set and IPS+R

The final step of the deliverable involved the use of the Core Data Element Set and the emerging IPS for use in clinical research (IPS+R). Specifically, leveraging the work from WP5.2 and the deliverable D5.1 titled 'D5.1 Proposal for a harmonized core data set across health care, population health, and clinical research,' the harmonized core data set was considered in the context of the selected BUCs.

This core data element set is designed especially to support clinical research. The core element set was assessed for relevance across different BUC with the identification of the data selected for the BUC and the intend to work towards IPS+R.

2. Results

2.1 Business use case choices

The field of clinical research is large and many different business use cases would benefit of being studied in the project. The first step of work with the Working Group (WG) was to brainstorm about the different business use cases in the scope of task 5.1 where business use cases will be analyzed with focus on real-world data items of greatest value to clinical research and proposals for a research extension to the IPS (IPS+R). A global list of 10 BUC has been suggested by the working group.

2.1.1 Listing of Use Cases

Use case 1: Patient pre-screening in clinical trial through healthcare professional pre-screening tool.

This BUC refers to patient's assessment of potential eligibility (pre-screening) in a clinical trial through a healthcare professional (HCP) tool for prescreening. This use case suggests automating the patient prescreening by a prescreening tool thanks to the data shared in the EEHRxF and made possible by the xShare Button.

Use case 2: Patient self-nomination as possibly eligible for a trial.

This use case is about the patient self-nomination as possibly eligible for a clinical trial. In this use case, the patient is the main actor to find the ongoing clinical trial compliant with their health profile, thanks to the xShare Button, and allows communication with the investigation site.

Use case 3: Protocol feasibility via a repository of IPS+R summaries, e.g. at hospital, regional or national level

This use case is about the possibility to perform protocol feasibility (methodology, eligibility criteria, site selection) via a repository of IPS+R summaries. It is proposing to use the EEHRxF to build queries able to extract study feasibility data from repositories.

Use case 4: Targeted patient recruitment via a repository of IPS+R summaries, e.g. at hospital, regional or national level

This use case refers to the selection of patients via a repository of IPS+R summaries in order to do targeted recruitment. In this use case, the patient prescreening can be done at different levels directly through repositories.

Use case 5: Clinical Study support – whole scenario (side effect reporting)

This use case refers to clinical study support, during the clinical realization phase, for the side effect reporting in a clinical trial. It suggests the automatization of the data reporting in a clinical trial thanks to the xShare Button data sharing in the EEHRxF.

Use case 6: Longitudinal cohort tracking

This use case refers to tracking for longitudinal cohort. It uses the IPS+R at the EEHRxF to create a cohort of patients in a defined geographical area.

Use case 7: Clinical Study definition

This use case is related to clinical study definition in terms of IT system. It uses repositories to specify the data set needed for the eCRF.

Use case 8: Clinical Study follow-ups

This use case refers to prospective clinical study follow-up (e.g. Filling up a questionnaire every 2 months). The xShare Button allows the automatic filling by data transfer/sharing of data related to a clinical trial management system.

Use case 9: Site feasibility guided by the xShare Button

This use case refers to site feasibility guided by the xShare Button and one of more repositories of IPS+R summaries. The EEHRxF data sharing allows the selection of sites participation into a study regarding their current active file.

Use case 10: eCRF Filling Process through xShare Button

The last use case is the automatic eCRF filling thanks to the xShare Button. The xShare Button automatize the data entry for a clinical trial in an eCRF from the IPS+R.

2.1.2 Votes

The use cases suggested by the working group are all of interest and some of them share common elements. The 10 BUCs have been regrouped in 4 main categories: Study feasibility, Pre-screening, Study support and Cohort and the classification is presented in *Table 1*.

Table 1 : Business use case scope classification

N°	BUC Title	Scope
1	Patient pre-screening in clinical trial through the CT-SCOUT healthcare professional tool	Prescreening
2	Patient self-nomination as possibly eligible for a trial	Prescreening
3	Protocol feasibility via a repository of IPS+R summaries, e.g. at hospital, regional or national level	Feasibility
4	Targeted patient recruitment via a repository of IPS+R summaries, e.g. at hospital, regional or national level	Prescreening
5	Clinical Study support – whole scenario (side effect reporting)	Study support
6	Longitudinal cohort tracking	Cohort
7	Clinical Study definition	Study support

N°	BUC Title	Scope
8	Clinical Study follow-ups	Study support
9	Site feasibility guided by xShare Button	Feasibility
10	eCRF Filling Process through xShare Button	Study support

Three BUCs refer to the pre-screening process, offering suggestions to facilitate patient selection for clinical trials. This can be achieved through repositories, healthcare provider actions, or patient initiatives. Two BUCs focus on clinical trial feasibility, addressing protocol and site selection considerations before launching a clinical trial. Four BUCs pertain to study support, encompassing tasks during the clinical operation phase, such as data entry and database definition. The final BUC involves the creation of a longitudinal cohort. Although this is an interesting application of the xShare Yellow Button, the WG decided that this use case is not in the scope of this deliverable as the major challenges in clinical trials are related to other studies' methodologies.

Figure 2 presents the voting results for the different BUCs from the WG and illustrates the distribution of votes across various BUC scopes. The voting results are as follows:

- 25% of the votes were allocated to the two BUCs related to patient pre-screening for clinical trials.
- 37% of the votes were distributed among the four BUCs related to study support.
- 38% of the votes were for BUCs related to clinical trial feasibility. Notably, 25% of the votes within this category were specifically for the protocol feasibility BUC (BUC3).

This distribution highlights the WG's prioritization of BUCs that address critical aspects of clinical trial processes, ensuring a focused and effective analysis within the scope of this deliverable.

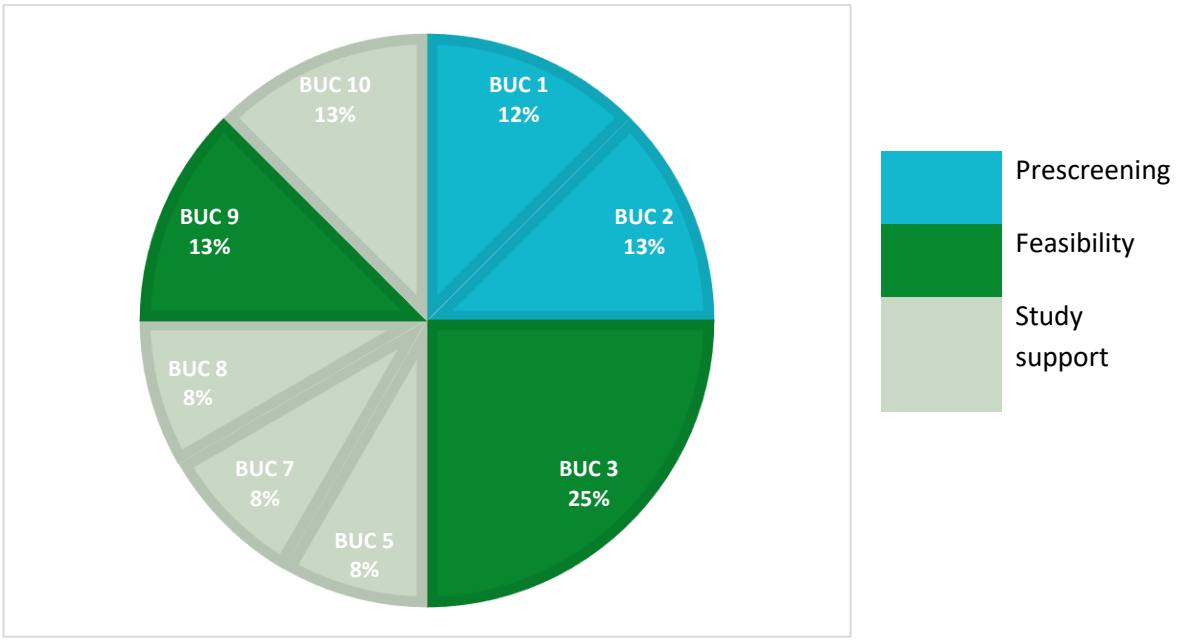

Figure 2: BUC votes results and scope

BUC 3, which focuses on 'Protocol feasibility via a repository of IPS+R summaries' at the hospital, regional, or national level, received the highest proportion of votes. Consequently, This BUC will be studied in-depth by the WG for this deliverable. If possible, the scope of this BUC will also be extended to site selection in order to cover a large range of business opportunities.

The working group's deliberation led to the selection of two additional BUCs—one related to patient pre-screening and another related to study support to cover all the BUCs scopes.

For pre-screening, the choice was between BUC 1 ('Patient pre-screening in clinical trials through the CT-SCOUT healthcare professional tool') and BUC 2 ('Patient self-nomination as possibly eligible for a trial'). Notably, BUC 2 shares similarities with BUC 3.3.8 (Adoption sites - xShare Button in products aspiring to be part of the French myHealth space ecosystem). Ultimately, BUC 2 was chosen due to its patient empowerment and alignment with the xShare project's objectives.

Regarding study support, BUC 5 ('Clinical Study support – whole scenario' with side effect reporting) offers the most value because of the complexity of adverse event reporting in clinical trial and the critical aspect of this process for the patient's safety. Additionally, BUC 10 ('eCRF Filling Process through xShare Button') received significant support within the study scope and would be a very interesting way to highlight the use of the xShare Yellow Button. As a result, a recommendation was made by the working group to merge BUC 5 and BUC 10, creating a new BUC that explores prefilling adverse event data in clinical trials.

2.2 Protocol feasibility via a repository of IPS+R summaries, e.g. at hospital, regional or national level

2.2.1 Feasibility: Overall description of the BUC

2.2.1.1 Context and Business goal

This business use case enriches an existing (operational) use case that was pioneered over 10 years ago and is now a commercial reality. (De Moor G, 2015)

This provides the capability for a pharmaceutical industry clinical trial protocol designer to connect through a third-party Information and Communication Technology (ICT) platform company and perform distributed queries on multiple hospital electronic health record systems. The protocol designer is able to compose a query based on candidate protocol eligibility criteria, and to discover through frequency distributions (without any patient level data) the location of potentially eligible patients across a network of hospitals within one or multiple countries. This allows the protocol to be refined to maximize the likely recruitment of suitable patients and provide insights into which hospital sites are likely to have a viable number of eligible patients. This pre-existing use case is gaining traction across many parts of the world, having started in Europe and the US. However, its scalability limitation is the number of hospitals that third-party ICT companies can connect to, which has both technical and governance site-specific challenges, and on the quality of the relevant data elements in the EHR systems.

This xShare Business Use Case leverages the anticipated investments that will take place all over Europe by Member States through the European Health Data Space Regulation to implement interoperability interfaces to all of their deployed EHR systems focusing on the EEHRxF, which we hope in future will include the IPS+R. The IPS+R contains the data elements of greatest likelihood of relevance to clinical protocol designers and their eligibility criteria. It is expected that Member States will establish national or regional repositories of IPS+R data, which could provide a more tractable solution for large (population) scale queries in order to optimize protocols at a country level and to find potentially relevant patients across a whole country in a single process.

The purpose is to scale up in a practical and affordable way the penetration of the capability for federated EHR querying, to optimize clinical trial protocols and to case-find potentially relevant sites and patients, within European countries. Moreover, this use case will be of greatest value and impact for the target group and additional stakeholders if it is adopted across Europe, and preferably globally. However, uptake is likely to occur country by country. The penetration of hospital EHR data access for clinical trial purposes is currently patchy and limited compared to the number of hospitals that could potentially have relevant patients and be utilized for recruitment.

If this use case was deployed across a substantial number of hospitals and health centers, it could revolutionize the way clinical trial protocols are developed. By assessing the impact of each eligibility criterion on recruitment, we could gain a robust understanding of the recruitment capabilities of a hospital interested in becoming an investigation site.

The principal actors in this BUC are:

- Target group: Pharmaceutical industry. The medical devices and AI development sectors might also find this BUC of interest.
- Stakeholders: Hospitals, which would have the potential to increase their clinical trial activity and consequent revenue from clinical research. Patients will benefit from the availability of new treatments and technology that they would not have had access to previously (i.e. to make trials more inclusive). It is possible that healthcare systems will benefit downstream from a lower cost of drug development, through lower pricing.

2.2.1.2 Process & flow

The critical on-the-ground change, and an open issue, that is needed for this BUC to succeed is the deployment of national/regional repositories of patient health data including the IPS+R data elements, with good population coverage, of a reasonably high-quality and kept up-to-date, that is open to federated querying by industry for clinical trial design and recruitment purposes.

Table 2 describes the study feasibility BUC process from preconditions to post conditions and *Figure 3* illustrates the flow.

Table 2 : BUC feasibility process

Steps	Description
Preconditions	The main precondition will be the agreement by the European Commission (EC) and Member States to adopt the IPS+R as part of the EEHRxF.
Trigger	Multi-stakeholder endorsement of the xShare IPS+R specifications as correct, relevant, practical and useful for the future of healthcare, treatment innovation and health systems sustainability.
Flow	0 (Precondition). The IPS+R is endorsed by Member States and the EC to be part of the EEHRxF, possibly also recommending this to ISO for the next version of the IPS. 1. Ministries of health and health insurers incentivize hospitals and general practitioner practices to maximize the quality of IPS+R data elements, through staff training, improvements to EHR systems, KPIs etc. 2. EHR system vendors implement and upgrade deployment sites with: • IPS+R import export interfaces • data quality metrics on IPS+R data within their repositories • user interface and data entry workflow support to optimize the completeness and accuracy of IPS+R data elements (e.g. a prompt to add a new diagnosis to the summary)

Steps	Description
	3. Regional and national health systems establish population repositories of IPS+R data (and other exchange format data) and processes to maintain its currency from different healthcare provider systems. These are 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+R 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. ICT companies making clinical research platforms implement federated query channels to these new repositories and update query tools for protocol designers and recruitment personnel. 7. Pharma companies contract with these companies, train relevant staff and adapt their workflows to leverage EHR data for clinical trial design and recruitment scenarios.
Post conditions	This BUC already contains almost all of the necessary post conditions. It will be necessary for the Pharma industry to adapt its present methods for clinical trial protocol design, site selection and patient recruitment in order to take advantage of this solution. This may also have personnel training implications.

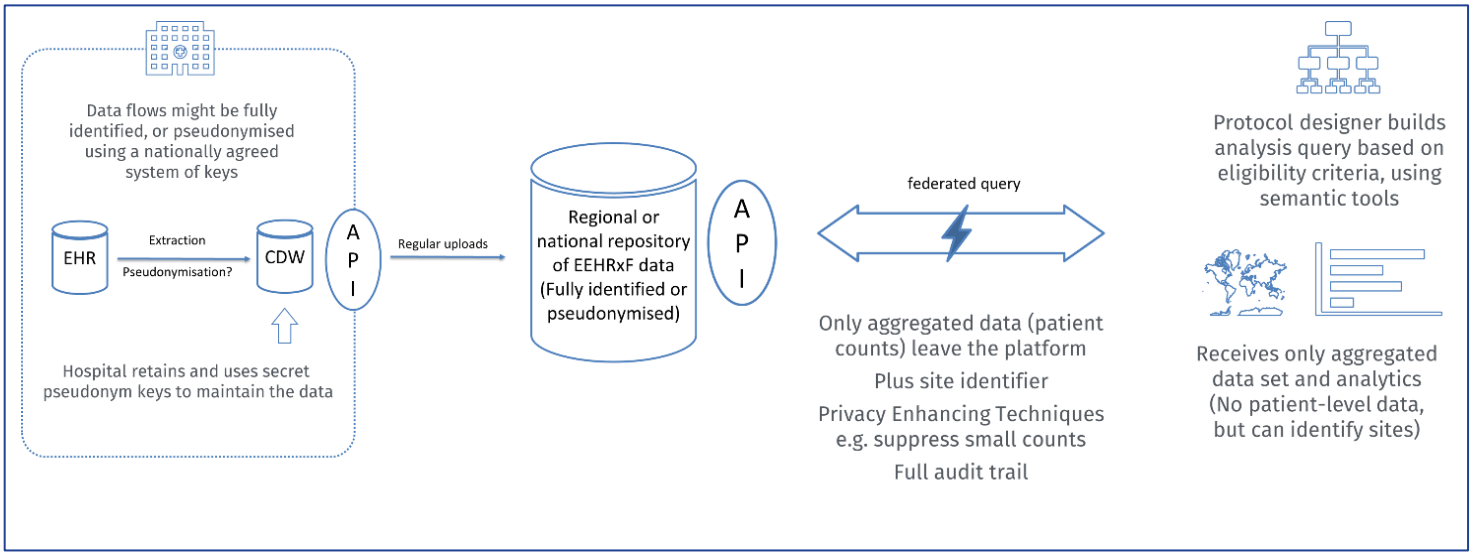

Figure 3 : Feasibility BUC Flowchart

2.2.2 Feasibility: User Stories

The primary (first mover) actor required for this BUC is Member States, and the EC, to promote and invest in the rapid uptake of the EEHRxF by healthcare provider EHR systems, and the implementation of large-scale data repositories of the priority data categories. Their role will be the definition of policy, funding, incentivization, orchestration. The feasibility assessment of their protocols will benefit the pharma industry.

The user stories suggested for this BUC are categorized into three levels of relevance and are presented in the *Table 3*. The first and most important category is the "critical" one and in which six user stories have been suggested from the perspectives of a Pharma protocol designer/manager, CT investigator, patient, hospital CEO, health ICT company, and member states. The second category classified as "important", includes five user stories. These stories pertain to a Pharma protocol designer/manager, Pharma company executive, hospital CEO, and healthcare payer. Lastly, the "not so important" category includes user stories from the perspective of a hospital CEO.

Table 3 : Feasibility User Stories

AS A (WHO)	**I WANT (WHAT)**	**SO THAT (WHY)**	**Relevance**
Pharma protocol designer/manager	To know if my protocol eligibility criteria are likely to yield enough patients	To be confident of having sufficient recruitment for a viable clinical study that will complete on time and on target	Critical

AS A (WHO)	I WANT (WHAT)	SO THAT (WHY)	Relevance
Pharma protocol designer/manager	To know which clinical sites have the greatest likelihood of recruiting a substantial number of patients, making them viable to open as trial sites	To maximize the likelihood of sufficient study recruitment without wasting time, effort and resources on sites that will not be able to recruit many patients	Critical
Pharma protocol designer/manager	To be as precise as possible in specifying inclusion and exclusion criteria	To maximize the scientific rigor of the study, without compromising on study numbers	Critical
Pharma company executive	To be able to conduct clinical studies in as wide a geographic area as possible at the lowest possible cost	To maximize the regulatory acceptability of the study without involving countries that are unlikely to be successful at finding suitable patients	Important
Clinical trial investigator	To be able to predict with reasonable accuracy the number of patients I should be able to recruit to study, to enable me to select those studies to undertake at which my site will be successful	To have a good reputation as a successful clinical site, and to enhance my reputation and to be attractive for the placement of future clinical studies	Critical
Hospital CEO	To be able to conduct a large number of industry sponsored clinical trials as cost-effectively as possible	To be attractive to industry sponsors as a future study site to provide their community of patients with the latest science and technology at minimal cost.	Important
Hospital CEO	To be recognized as a successful clinical research hospital	To be attractive to the brightest new doctors and other health professionals	Critical
Hospital CEO	To have a strong research driver for having good data quality within our EHR system	To add research as an incentive for improved data quality which will enhance and enable the analytics and improve the quality health systems data which in turn will provide insight into the quality of care and improvement opportunities as a side benefit.	Not so important
Patient	To be able to participate in a clinical trial that is an applicable to me	To avoid the false hope of being invited to participate in a trial for which I prove not to be eligible	Critical

AS A (WHO)	I WANT (WHAT)	SO THAT (WHY)	Relevance
Healthcare payer	To enable drug development in my country to be cost-effective	To enable my health system to access innovative medicines at the lowest possible price	Important
Health ICT company	To find wide-scale pharma interest in reusing EHR data for clinical research	To have a strong market for my research platform products	Critical
Member State	To have an efficient and high-level quality IPS+R repository	To be an attractive area for clinical research industry	Critical

2.2.3 Feasibility: Overlap with IPS

The health information content relevant to this use case is based on the core element set of D5.1 and paves the way towards the intended xShare proposed IPS+R. It expands the existing ISO IPS data elements by adding demographic details about the data subject, healthcare encounters, medication details and adverse event details.

The complete overlap between data expected from this BUC and the xShare data element set proposed in deliverable 5.1 is available in the Appendix II: Overlap with IPS.

Some data are not required from IPS category Subject, those related to the Study identifier and subject identifier, as at the stage of feasibility, the protocol does not exist yet and no patient is included.

Otherwise, all the data suggested in the xShare core data element set are either required or optional but would benefit the business use case.

Figure 4 presents the proportion of data from the core data elements set required for the execution of the BUC. A large portion (79%) of the core data from this set is required, a few core elements are optional (7%), and only a small portion (14%) is not required.

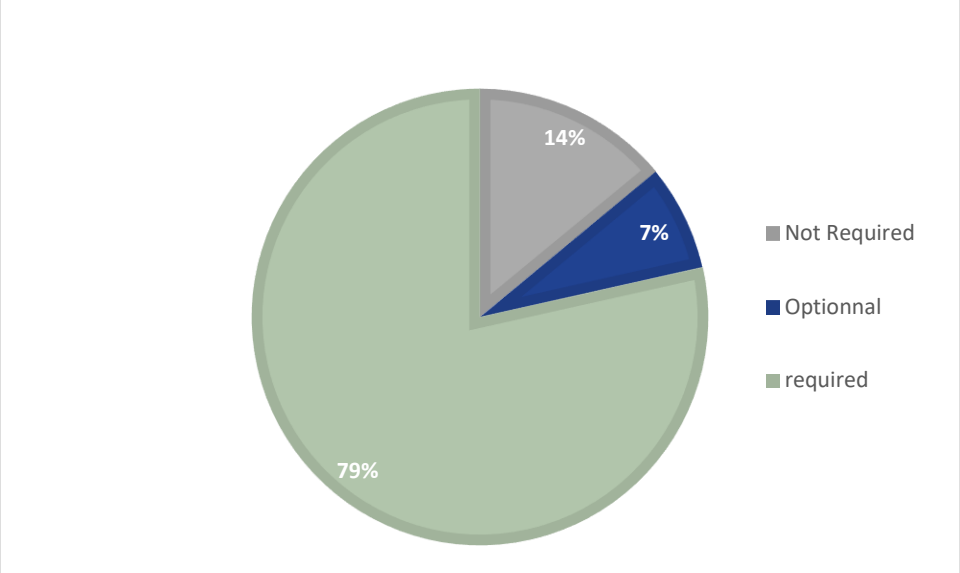

Figure 4 : Percentage of core data element from core element set needed for the study feasibility BUC according to the level of requirement

2.3 Patient self-nomination as possibly eligible for prescreening in a trial thanks to the xShare Button

2.3.1 Prescreening: Overall description of the BUC

2.3.1.1 Context and business goal

Patient recruitment is one of the most challenging aspects of conducting clinical trials. The initial step in this process is pre-screening, which occurs before patients provide their ICF. During pre-screening, the investigative team actively reviews the patient's EHR to assess compatibility with the ongoing clinical trial, based on available data and the patient's profile. If eligible, the patient is contacted and invited to participate in the study. Additionally, prescreening can be seamlessly integrated into routine medical consultations at the center. Both approaches involve proactive actions by members of the investigative team and do not involve the patient.

This business use case focuses on empowering patients to explore potential clinical studies by leveraging their health data. Whether it is a patient with limited therapeutic options or a health-conscious volunteer, anyone can express interest in participating in a clinical trial. However, there currently is not a democratic way for individuals to assess their eligibility based on their health data. To address this gap, it should be considered to develop an application that allows patients to utilize the xShare Yellow Button for health data sharing of the IPS at the EEHRxF and initiate eligibility assessment. By streamlining the pre-screening process, this innovative approach would create a new recruitment channel, directly impacting the effectiveness of trials.

This scenario involves the availability of an application for patients and healthy volunteers to access their health data, specifically the PHR. Some countries, such as France with its "mon espace santé," already have PHR apps. This topic is also relevant to another BUC related to WP3.1 – French adoption site. The new electronic cross-border health service, MyHealth@EU, could serve as the ideal tool for creating a global PHR app at the European level, eliminating the need for country-specific specifications. The PHR app would greatly benefit from the inclusion of an xShare Yellow Button. This Button would allow users to share data from their EHR in the EEHRxF with a prescreening tool. This tool could then filter potential compatible clinical studies based on the patient and healthy volunteer's IPS. By automating data input and enhancing the relevant health information available, the app would improve the assessment of potential eligibility for clinical trials.

This use case implies interaction with study registries where there is a link between the ongoing clinical trial, the hospital participating in the trial and the prescreening tool. This link can be performed by the prescreening tool (IT vendor). It also implies the mapping of health data from the IPS and the prescreening tool questionnaire. (e.g. subject demographic = age, the patient must be between 18 and 75 years old to participate). Once the detection of potentially compatible clinical trial with the patient/ healthy volunteer, a percentage matches for the citizen to determine how compatible they may be with the current clinical trial (e.g. the pre-screening is 80% compatible with the study eligibility criteria, the remaining 20% is unknown data such as non-IPS data, only the on-site team would be able to complete and evaluate the full patient pre-screening).

This use case will be of greatest value and impact for the target group and additional stakeholders if it is adopted across Europe, and preferably globally. The possibility of implementing this use case on a cross-border scale would be particularly relevant in the field of rare disease and to people living close to a border.

The purpose is to scale up with an automatic and high-level quality way to assess the patient potential eligibility compatibility to a CT, to optimize clinical trial recruitment and to accelerate CT.

The principal actors in this BUC are:

- Target group: The main target group of this use case is the citizen, with either patients willing to participate to a clinical trial depending on their health condition (to some extent parents, or caregivers) or healthy volunteers willing to participate to a clinical trial to help advance science. The second target group is the on-site clinical investigation team willing to improve their recruitment by receiving patients coming from pre-screening tools.
- Stakeholders: This is in the first place the Sponsor/CRO willing to improve recruitment to their studies by extending them to patients outside the hospital. But also, the Clinical trial registry (EudraCT, CTIS, CT.gov, WHO ICTRP), the European/National/local provider of health data space/app and the IT vendor developing a pre-screening tool and other product related features.

2.3.1.2 Process & flow

The critical on-the-ground change that is needed for this BUC to succeed is for the patient/healthy volunteer to access a PHR containing structured data (EEHRxF) linked to the IPS with automated upload of health information (+ possibility to manually add complementary information), such as the national apps or MyHealth@EU. This PHR app would include the xShare Yellow Button. And the mapping between data at EEHRxF from the IPS to the pre-screening tool questionnaire.

Table 4 describes the prescreening BUC process from preconditions to post conditions and *Figure 5* illustrates the flow.

Table 4 : Prescreening BUC process

Steps	Description
Preconditions	There are two major preconditions to the execution of this BUC. The first one is the existence of a PHR app connected to national / regional infrastructure (i.e. MyHealth@EU, Mon Espace Santé (French app) etc.) and the second one is the fact that health data needed for the prescreening must be available in the IPS (IPS+R) and able to be mobilized for mapping.
Trigger	A citizen wants to know if they are possibly eligible for a clinical trial.
Flow	Patients/healthy volunteers have access to a PHR app to access their health data and in 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. Basic flow Steps: 1. The user accesses to the PHR app (The data format is EEHRxF/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 prescreening application and mapped with prescreening questions 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 centers are accessible to the patient, including a percentage of compatibility. 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 center. 7. The user gives consent for their data sharing (Access to the IPS, IPS+R) by the chosen center.

Steps	Description
	8. The center 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 center accesses the user's pre-screening data. 10. The center 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. (Number of visits, invasive exam...) 11. The user full eligibility is assessed by the site during the onsite visit. Alternative workflow N°1: The patient/healthy volunteer health condition changes and the results of compatible studies are updated accordingly. Alternative workflow N°2: There was no match between the patient/healthy volunteers and a clinical trial. When new studies have been updated the patient/healthy volunteer is informed.
Post conditions	To ensure the continuity of this BUC until the patient's inclusion, the study team must engage with and take care of the candidate for the clinical trial. In addition, and to be compliant with the GDPR, patient / healthy volunteers must have the possibility to: • Limit the Access to their data but still receive the update of new ongoing clinical trial in the hospital of their choice, • Stop the access to their data but maintain the PHR app access, • Delete any data sharing that could have been performed to assess the potential eligibility An additional post condition is the secondary use of the global prescreening data for population health data analysis and research. This condition must be clearly defined. Finally, the status update according to the changes in the medical profile or the ongoing clinical trials applying for linked option will have to be defined.

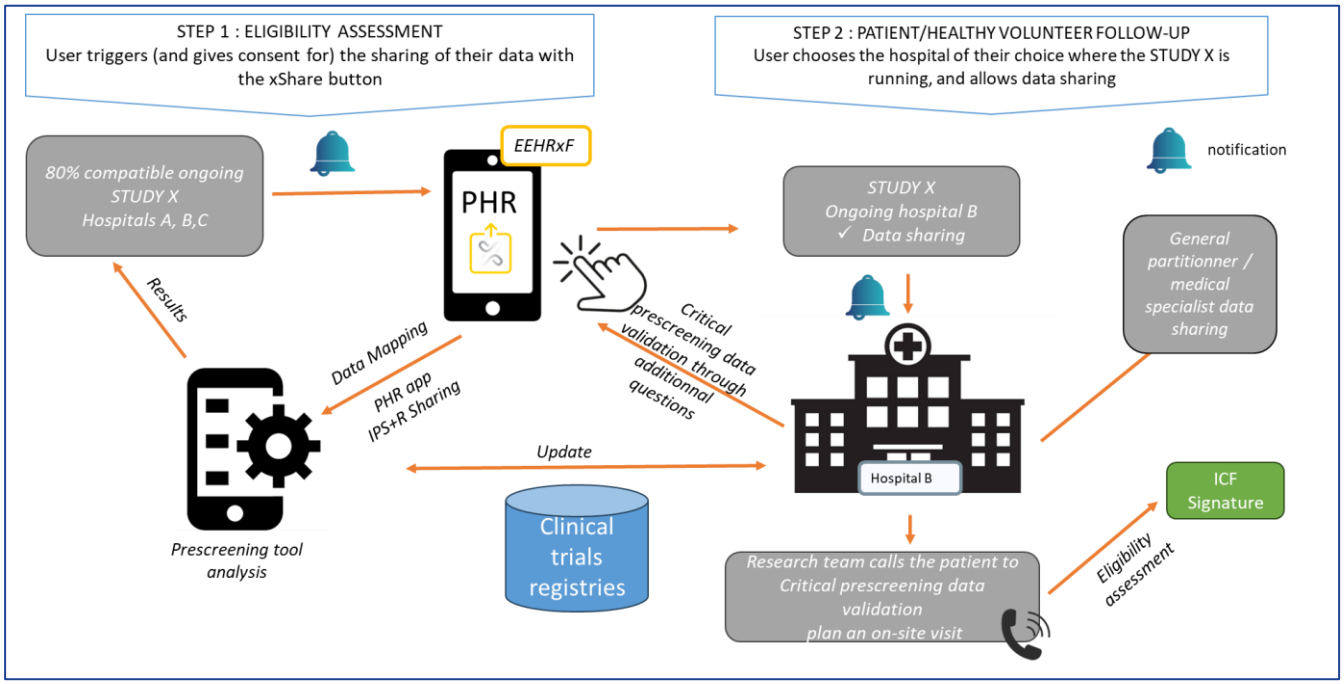

Figure 5 : BUC prescreening Flow

2.3.2 Prescreening: User stories

The primary user will be a patient or the healthy volunteer willing to be involved in a clinical trial. For the vulnerable population (under 18, under guardianship etc.), parents or care givers will be primary users. The second beneficiary of this use case will be the investigation team on site which will take charge of the user and receive help by this process for the recruitment of their patients. The last beneficiary will by the sponsor/CRO providing the CT in which one of the end users is potentially eligible for improved and more efficient recruitment in their studies, leading to a reduction of costs.

The user stories suggested for this BUC are categorized into three levels of relevance and presented in *Table 5.* The first and most important category is classified as “critical”. Six user stories have been suggested from the perspectives of a patient/healthy volunteer and clinical investigator. The second category, “important”, includes fifteen user stories. These stories pertain to a patient/healthy volunteer, clinical investigator and also the research team and the sponsor. No classified as “not so important” user story has been proposed.

These user stories refer to different data sources, depending on the actor of the story. For the patient as an actor, data source is the IPS+R, the GDPR, the hospital location, the clinical trial list and the CT information. Moreover, most of the patients’ user stories are related to the PHR application (on mobile device) or site related information.

Table 5 : Prescreening User stories

AS A (WHO)	I WANT (WHAT)	SO THAT (WHY)	Relevance
Patient/ healthy volunteer	Share a selection of personal health data related to my condition to a clinical investigator	A clinical investigator can evaluate if I can be potentially eligible for a clinical trial.	Critical
Patient/ healthy volunteer	Be contacted if a new clinical trial matches my health profile	A clinical investigator can evaluate if I can be potentially eligible for the new clinical trial.	Critical
Patient/ healthy volunteer	Be able to choose the hospital in which a clinical trial matches my health profile	A clinical investigator can evaluate if I can be potentially eligible for a clinical trial in the hospital of my choice.	Important
Patient/ healthy volunteer	Know how my data will be used and by whom	I can exercise my data portability rights under GDPR	Critical
Patient/ healthy volunteer	Know which data will be used	I can exercise my data portability rights under GDPR	Critical
Patient/ healthy volunteer	Be able to get an appointment at the hospital of my choice in which a clinical trial matches my health profile	My full eligibility can be evaluated by a clinical investigator during a medical visit	Important
Patient/ healthy volunteer	Modify/delete the access to my data	I can exercise my data portability rights under GDPR	Important
Patient/ healthy volunteer	Be informed of the clinical trial matching my health profile	I can evaluate my interest to participate in the clinical trial	Important
Patient/ healthy volunteer	Get more information about the clinical trial matching my health profile	I can evaluate my interest to participate to the clinical trial	Important
Clinical investigator	Know if new patients are potentially eligible to clinical trial ongoing at my hospital	I can propose them to participate	Critical
Clinical investigator	Be able to get the patient coming at my hospital	I can evaluate the eligibility during a medical visit	Critical
Clinical investigator	Be able to find my patient data previously/during the medical visit	I can save time in the patient eligibility assessment to my ongoing clinical trials	Important
Clinical investigator	Be able to refer the patient to my research team	The patient can be followed up for their potential inclusion in the clinical trial	Important
Clinical investigator	Have access to the potentially eligible full patient summary (IPS+R)	I can save time in the patient full eligibility assessment to my ongoing clinical trials	Important
Research team	Be informed when a new patient is potentially eligible for clinical trial ongoing at my hospital	I can follow up the patient for their potential inclusion in the clinical trial	Important

AS A (WHO)	I WANT (WHAT)	SO THAT (WHY)	Relevance
Research team	Have access to the potentially eligible full patient summary (IPS+R)	I can save time in the screening process	Important
Research team	Be able to get the potentially eligible patient coming at my investigation site	The patient eligibility can be evaluated during a medical visit	Important
Patient/ healthy volunteer	Share my full patient summary	Their full eligibility to a clinical trial can be evaluated by Clinical investigator/research team	Important
Sponsor	To share my ongoing studies with the prescreening tool	I can improve the recruitment efficiency of my studies	Important
Sponsor	To share the ongoing studies sites	I can improve the recruitment efficiency of my studies	Important
Clinical investigator/ research team	My clinical studies to be automatically updated based on recruitment starting and ending date	I can avoid any wrong patient referral	Important

2.3.3 Prescreening: Overlap with IPS

The health information content relevant for this use case is related to the core element set, described in the Deliverable 5.1. However specific data for research provided through the core element set are not needed at prescreening level, but the work should be initiated with the IPS and enriched with IPS+R as it is specified. A complete IPS would be needed, including the optional fields (ex: pregnancy status). If the level of information available in the IPS is not sufficient for prescreening, a note will appear for the patient/healthy volunteer to add the data or stop the process.

The complete overlap between data expected from this BUC and the xShare data element set proposed in deliverable 5.1 is available in the Appendix II: Overlap with IPS.

Figure 6 presents the proportion of data from the xShare core data elements required for the execution of the BUC. Around half of the data set is either required (45%) or not required (45%). The important proposition of data not required for this use case is explained by the methodology of the pre-screening. Indeed, the patient potential assessment eligibility before the ICF signature is based on basic end generic health data, it must be performed with the most common available data to be efficient. Then 10% of the data set are recommended or optional data in equal part and would depend on the pathology studied or the protocol methodology.

It should be noticed that some data indicated as “required” can be substituted by other required data. For example, to perform the patient pre-screening it is important to know the age of the patient. This information is available with the data element “age”+”collection date” or “birth date”, only one of the

data sources will be relevant for the use case but both sources are compatible to answer to the need. This comment will be true for all the data referring to an event duration or a start and end date.

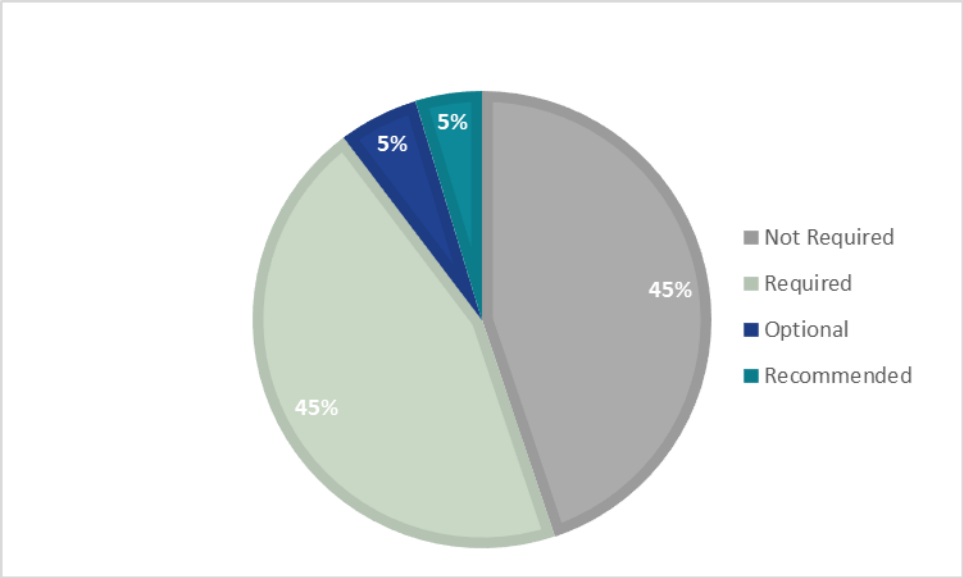

Figure 6: Percentage of core data elements from IPS+R needed for the prescreening BUC according to the level of requirement

2.4 Support for data collection of a health study

2.4.1 Study support: Overall description of the BUC

2.4.1.1 Context and Business goal

The main purpose of this BUC is to define how to leverage existing health data to support data collection defined in a health study (clinical study, epidemiological study) in a population of enrolled patients, where the selection criteria was verified and the appropriate consent for data management was acquired to meet regulatory requirements and local policies. Data collections exploit the definition of EEHRxF and the implementation of the xShare Button.

Citizens' health data is present in EHR, EMR and PHR systems, but also in Clinical Data Warehouses, Patient registries, Diseases networks, FAIR data repositories, etc. Those 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 the provenances management.

Processes that simplify data collection and technologies that meet data protection regulatory requirements are necessary prerequisites for the reuse of health data for research and enhance trust building in the final users (both patients and researchers). These aspects are addressed with the usage of a common standard EEHRxF and its associated controlled terminologies for the semantical aspects,

adopted also to tackle the problem of connecting regional diversity in languages, healthcare practices and regulations, now affecting most of the Hospitals/healthcare provider that can contribute to research.

This BUC comprehends technical, standards, functional, legal, and organizational aspects, not all details of each aspect are reported in the description. This BUC starts after the definition of the study and its CRF, and the formal eligibility criteria to allow computer-assisted checking of patient eligibility, the engagement of the research/healthcare organization and the patient enrolment.

The health study design includes the definition of a CRF, implemented in its electronic version as an IT system referred as eCRF available at researcher's site, whose items should be mapped with the interoperable data sources available in the data collection environment (Investigation sites: Hospital, research center, etc). The xShare Button is actioned by the patient enrolled in a study, and it prepares and sends to the research center/sponsor the EEHRxF/IPS+R subset of information available through patient's devices (PHR, etc) as required and mapped on the study's eCRF.

This use case will be of greatest value and impact for the target group and additional stakeholders if it is adopted across Europe, and preferably globally. The scale of the BUC will have to be the same as the study, e.g., a national study will benefit from a national scope with no need for cross-border.

The purpose of this BUC is to support and simplify the data collection defined in a retrospective and/or prospective observational health study, while maximizing data quality. This BUC could be expanded to prospective interventional studies but would require additional data protection/management not described in the scope of this use case. Support data collection for health studies is based on the definition of an eCRF (also trough the xShare Button). This will facilitate data collection both for patients and researchers, reduce the cost of data ingestion and increase data collection quality.

- Target group: The first target group is the patient/healthy volunteers included in a clinical trial and willing to take control over their health data, then the Investigative team with the Healthcare providers and the research team willing to increase the efficiency of their ongoing trials. In addition, sponsors (Academic, Industry, CRO, other (Gov)) willing to automatize their clinical trial data entry to get more efficient and high-level quality data in their clinical trials.
- Stakeholders: IT solutions such as system integrators and software that the IT team can provide to support the stakeholders.
-

2.4.1.2 Process and Flow

The critical on-the-ground change that is needed for this BUC to succeed is that each study shall define an electronic format of the CRF, expressed in the EEHRxF standard. A similar use case can be found in the CDISC and IHE's Retrieve Form for Data Capture (RFD) specification. This specification was developed to allow for the exchange of data from an EHR to populate an eCRF. (REF - https://profiles.ihe.net/ITI/TF/Volume1/ch-17.html) The eCRF shall report: type of the study, study

sponsor, enrolment centers, enrolment criteria (and possible enrolment branches), and operational data such as collection period/frequency, health elements, exclusion criteria. A set of tools to map eCRF with data source systems (EHR/EMR/PHR/etc.) will help to connect each required item to real world data using EEHRxF. The creation of the xShare Button in systems under control of the patient, and implementing the eCRF mapping of a study, enable data transmission to the enrolment center/study sponsor.
Table 6 describes the study support BUC process from preconditions to post conditions and *Figure 7* illustrates the flow.

Table 6 :Study support BUC process

Steps	Description
Preconditions	This BUC requires several preconditions. The first one is that data is managed in a controlled and protected environment. The study will have to follow the regulation and methodology needed for a trial to be conducted in a defined center: - Approval of the study and the site by the respective/reference regulatory bodies in each country where the CT is ongoing. - eCRF design and definition for data collection. • Patient is identified as candidate by the center and is enrolled in a retrospective-prospective of the study; The patient signs the study ICF and data sharing permission only for the concerned study. The eCRF might contain elements beyond those defined in the core data element set and eventually IPS+R. eCRF elements are mapped with source IPS+R items, by the investigator systems (EHR) or by Data manager/EHR vendor/data source manager etc. The patient has access to a PHR App containing health data and IPS+R data. The PHR app enables the xShare Button for the defined study, to launch data sharing with the center.
Trigger	The patient wants to send Study X data.
Flow	The consenting patient enrolled in the study is included by the investigative team of the center. The Study allows eCRF automatic filling from of health data and the patient have access to their PHR app, containing a section allowing data sharing for clinical research. The patient agrees with the automatic health data filling the eCRF in the context of this study. Basic flow Steps:

Steps	Description
	• The Study team assists the patient to link their inclusion number to the study in the PHR App. • Patient allows, on the xShare Button (app allowing the data sharing between the IPS+R and the eCRF of study X), to send/share data to the study. 1. Health data from their IPS+R are mapped with the corresponding data in the eCRF. 2. IPS+R data are sent from the PHR to the eCRF of the study in the corresponding. • The investigative team of the research center receives the IPS+R data by the eCRF of the patient. The data from the IPS+R will not, in the scope of this BUC, allow the entire filling of the eCRF. • The investigation team completes the data collection missing according to the study X's eCRF and performs a manual or automatic quality control on the data collected. Alternative flow N°1 (retrospective/prospective study): A patient visit or examination occurs/occurred within the study context: the health data associated with that visit/examination are updated in the eCRF of the patient. Alternative Flow N°2 (cross-study data exchange): An examination or visit unrelated to the study X occurs while a patient is participating in a Study Y and results in an adverse event: the data related to the adverse event and required by the Study X are updated in the eCRF of the patient of the Study X. Alternative Flow N°3: The xShare Button used by a healthcare professional of an organization that supports the study to send enrolled patient's data, collected from the organization's EHRS/data sources, to the research center/sponsor.
Post conditions	Without explicit permission, data can be used only for the clinical protocols/studies granted by the patient with his/her consent. Another protocol requires another explicit permission. Upon patient's withdrawal request (data collection stops in prospective studies) the patient could require explicitly to delete collected information.

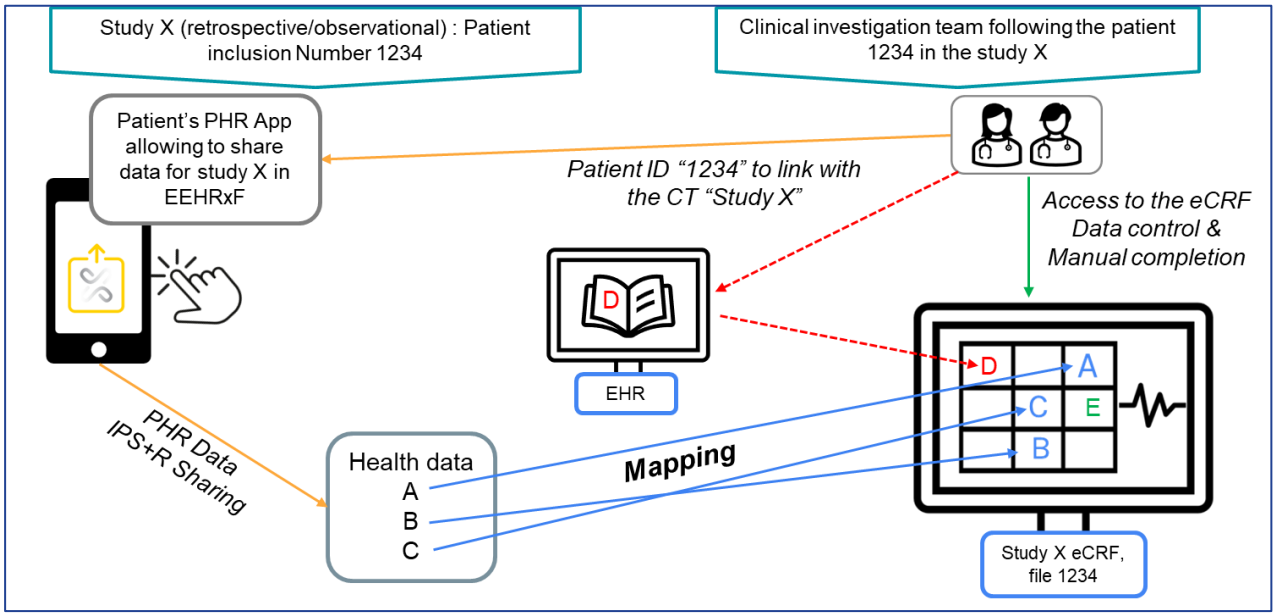

Figure 7 : Study support BUC flow chart

2.4.2 Study support: User stories

The primary user of this use case will be the patient or healthy volunteer included in a CT as the research subject and lead directly to the second user which is the investigation team benefiting from the automatic filling of the eCRF compared to the time-consuming manual data entry.

Organizations such as study sponsor, coordinator center, principal Investigator center or participating center will indirectly benefit from this use case by conducting an effective CT and respecting deadline and budget.

The user stories suggested for this BUC are categorized into three levels of relevance and presented in *Table 7.* The first and most important category is classified as "critical". Six user stories have been suggested from the perspectives of the research team, the patient and the sponsor. The second category, "important", includes four user stories. These stories pertain to a Citizen, clinical investigator and also the research team and the sponsor. No "not so important user story" has been proposed.

Table 7 : Study support user stories

AS A (WHO)	I WANT (WHAT)	SO THAT (WHY)	Relevance
Research team	To automatically collect the patient's medical personal data in the eCRF	I do not have to enter it manually and therefore save time	Critical
Citizen	To contribute anonymized data for a national health research project	I can advance public health research for the benefit of all	Important
Clinical investigator	Know the source of data collected	I can evaluate the quality and reliability of data entered in the CRF	Important
Sponsor	To monitor patient's eCRF flow globally/single center	I can get real time information on my clinical trial progress and run supportive actions at the site level	Important
Sponsor	Access real-time data from ongoing trials	We can make informed decisions about trial progression	Critical
Sponsor	To identify potential risks and ensure patient safety during research studies	I can make informed decisions about research protocols	Critical
Research team	To Check completed data on each patient's eCRF	I can activate the enrolled patient to add missing information (e.g. a patient's questionnaire)	Critical
Patient	I want to exercise my GDPR rights (edit, modify, delete)	I can control over the data I have shared	Critical
Research team	I want to link the patient eCRF with the patient in the PHR app	I am sure of the source of the data collected in the eCRF	Critical
Research team	I want the patient data from the EHR to be shared with the eCRF	I can complete the missing data	Important

2.4.3 Study support: Overlap with IPS

Considering the extremely variable range and specialization of data required in medical research, IPS+R could represent a reference base for research data ingestion, to be complemented with other EHR data and enhanced by data manually entered by the patient or health research team. The health information content relevant for this use case is a part of the xShare core element data set, described in the Deliverable 5.1.

The complete overlap between data expected from this BUC and the xShare data element set proposed in deliverable 5.1 in available in the Appendix II: Overlap with IPS.

Figure 8 presents the proportion of data from the xShare core data elements set required for the execution of the BUC. A large portion (78%) of the data from this set is required, a few elements are recommended (7%) or optional (13%), and only a very small portion (2%) is not required. The data not

required refers to ID for laboratory and microbiology, those data are not relevant in the scope of the eCRF. Otherwise, all the data of the xShare core data element set are relevant for this BUC. Indeed, eCRF are the reflects of clinical trial and can cover a very large range of pathologies, examinations and methodologies.

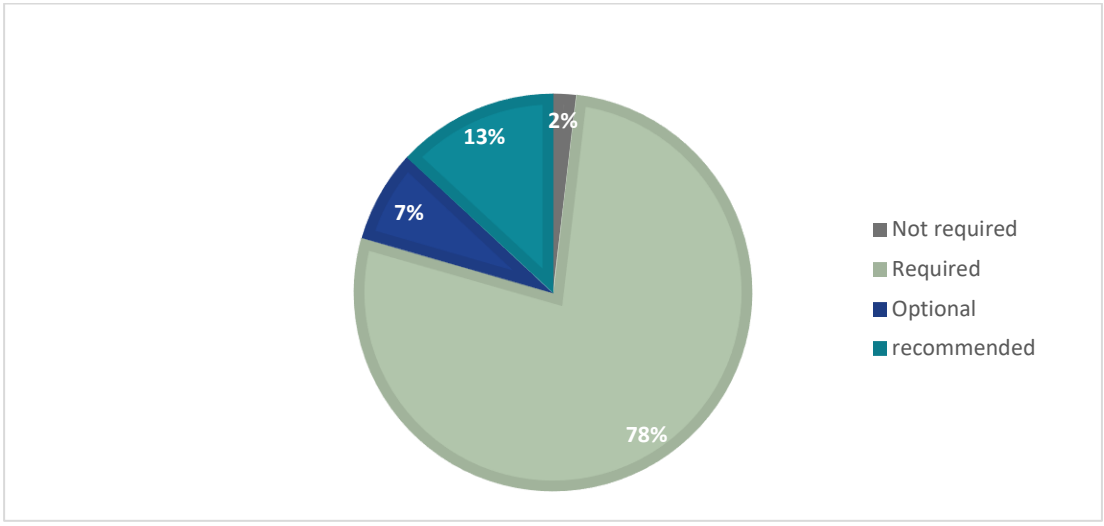

Figure 8: Percentage of core data elements from IPS+R needed for the study support BUC according to the level of requirement

3. Analysis

3.1 Use case analysis

Whether considering the list of BUCs envisioned by the Working Group or the three BUCs detailed in this report, the pre-patient inclusion phases—encompassing protocol conception and patient recruitment—pose the most significant challenge in clinical trials. The first two BUCs address patient recruitment difficulties. The first BUC, titled 'Protocol Feasibility via a Repository of IPS+R Summaries' (for example, at the hospital, regional, or national level), focuses on identifying the optimal protocol methodology and selecting investigation sites. The second BUC automates the initial phase of patient selection by allowing patients to self-nominate as potentially eligible for prescreening in a trial using the xShare Button. The third BUC tackles another common issue in clinical research: the time constraints faced by investigative teams. By streamlining administrative data entry, this new process enables the investigative team to prioritize the human aspect of their work—the patient follow-up.

3.1.1 BUC analysis: Protocol feasibility via a repository of IPS+R summaries, e.g. at hospital, regional or national level

This first business use case aims to allow protocol designers to improve the feasibility of their protocol. This BUC is well advanced because it enriches a pre-existing use case in the scope of a previous project (EHR4CT) which evaluated the use of EHR applied for clinical research. This use case's ambition is to leverage on to critical aspect of the clinical research which are the protocol eligibility criteria definition and by extension the site's selection in the context of study feasibility.

Indeed, site's selection is directly correlated to the future site's patient recruitment and well conduction of the clinical trial. The recruitment of patients for clinical trials is often complicated for several reasons. The first one is the fact that study protocols are becoming increasingly intricate. Researchers may seek patients with specific laboratory values based on blood analyses, information that patients typically do not know about themselves. This means that research sites exclude more patients during the selection process, leading to recruitment delays and challenging goal achievement. Then clinical trials cover a wide range of pathologies and populations. Finding specific patients for each study can be challenging due to significant patient characteristic variations. Moreover, coordinating between different research sites (hospitals, regional centers, national facilities) can be challenging. Each site must identify and recruit patients, leading to delays. This use case suggested querying the existing registries at a site level to ensure that the selected site has the potential to include the right number of patients with regards to their objectives.

Ultimately, effective patient recruitment requires a strategic approach from protocol design, involving stakeholders and training investigators. This will enhance the quality and efficiency of clinical trials. This use case also considers the protocol design by an approach based on the feasibility of the eligibility criteria on the population. Indeed, Inclusion and exclusion criteria defined in protocols can limit the number of eligible patients. Sometimes these criteria are overly restrictive, making it difficult to find suitable participants. This use case will allow to determine the most effective eligibility criteria.

This use case considers the development of the EHDS and the interoperability interface of EHR at the EEHRxF which aims to include the IPS+R. The xShare core data element set is very relevant as much data will be available the more precise the answer to the queries will be and the more adapted the site selection and protocol design will be. Indeed, 96% of the data from the data set are worth of interest in the scope of this BUC but it should be noticed that it does not take into consideration missing data, this means that some data out of the scope of the xShare data element set could also be of interest.

The primary beneficiary of this use case is the pharmaceutical protocol designer/manager. They gain access to critical information, enabling them to propose the most effective protocols. With confidence, they can recruit the right number of patients and achieve robust results during data analysis, addressing the primary outcome question. The functionality must allow query composition on the registries via EEHRxF. Additionally, pharma companies benefit from this information. It enables them to conduct studies with the optimal number of sites at the lowest cost, resulting in significant savings.

Hospital and investigation site CEOs will also take advantage of this use case. Having patients' EHR in the registries adds value to their sites. Effective clinical trials related to site-specific pathologies attract sponsors, aligning with objectives during ongoing CT trials. Clinical investigators contribute to the site's positive reputation and departmental success.

Furthermore, patients gain access to relevant clinical trials based on their health conditions as site selection considers the current active file. Healthcare payers benefit from cost-effective research development in the concerned country. Health ICT companies leverage this data to position products effectively in the market

This use case aims to enhance the feasibility of protocols by generating federated queries on repository upload by EHR health data information. This would allow the protocol designer to propose clinical trial in adequation with the patients regarding the eligibility criteria and with the investigation sites regarding the active file.

This use case goals are to:

- Promote the business and societal value of the IPS+R to Member States and the EU.
- Encourage Member States, by adding this use case and the pharmaceutical sector business interest to their existing drivers, to establish repositories of IPS+R data on their patient populations.
- Encourage, by adding this use case and the pharmaceutical sector business interest, Member States to incentivize and invest in data quality improvement strategies by hospitals, focusing on the IPS+R data.
- Enable the pharmaceutical sector to perform clinical trials in Europe more rapidly, at a lower cost and being more inclusive of members of the relevant patient populations.

However, major inhibitors to this investment will be a widespread perception that the EEHRxF and the EHDS primary use provisions are mainly relevant to cross border unplanned care. Since this is a low volume requirement for any national health system, this perception will limit the scale of investments

made to implement IPS+R interoperability and the national pooling of summaries. This has to be seen as of universal within- and cross- border value.

3.1.2 BUC analysis: Patient self-nomination as possibly eligible for prescreening in a trial thanks to the xShare Button

The ambition of this second business use case is to address a major challenge in clinical research: allowing patients to self-nominate for clinical trials. This self-nomination is integrated into the prescreening process, which occurs well before patient's inclusion and serves as the first step in selection. This phase is critical to ensuring effective patient recruitment for clinical trials.

Today, patients or even healthy volunteers willing to participate in clinical trials face significant barriers in assessing their potential eligibility and identifying ongoing trials in their area. Currently, prescreening is conducted by research teams at investigation sites. With their expertise or the aid of prescreening tools, these teams identify potentially eligible patients and propose participation in the trial. This process involves two major barriers. The first is the high-level time-consuming part of this task. Indeed, it is a manual and human task for the investigative team to research the EHR of the potential eligible patient; it is a targeted patient's prescreening based on the protocol of interest. The second barrier is the identification of a patient during a medical visit by the clinical investigator; the overall patient's prescreening requires the clinical investigator to have deep knowledge about the eligibility criteria of the clinical trials ongoing in the center. In both cases, the patient's motivation to be a part of a clinical trial, which is an indication of follow-up success, will be assessed during an on-site visit.

Research teams can utilize IT tools to help in patient pre-screening. One possibility for the medical team is to answer a short questionnaire about the patient's medical condition. This questionnaire, based on generic and specific health questions, can be used by all team members, even those not trained in clinical trials. As pre-screening occurs before inclusion and any additional exams, it relies on data available in the medical record.

Data of high-level quality and reliability is needed, and both the IPS and the future IPS+R provide valuable sources of information for filling out prescreening questionnaires. The section Prescreening: Overlap with IPS shows that the IPS contains more than enough data for prescreening, with only half of the proposed data set being relevant to this business use case.

Some generic data will always be of interest for patient prescreening, such as:

- Demographics: Information about the patient's age.
- Problem List: Medical history and reported terms, which should ideally be transcribed into ICD-10 code. ICD-10 is the international statistical classification of diseases and related health problems proposed by the World Health Organization (WHO), allowing each condition to have a unique code.

Depending on the pathology of interest for prescreening, only relevant data will be considered. For example:

- Diagnostic Results: Microbiology-related data would be relevant for clinical trials related to bacteriology or virology.

- Pregnancy Status, History & Summary: Pertinent for reproductive-related studies. However, pregnancy (except for pregnancy-related clinical trials) is typically an exclusion criterion, making it non-differentiating and irrelevant for most prescreening questionnaires. This status is always checked at the end of the screening process before inclusion to ensure safety.

Additionally, some data may be interesting depending on the methodology of the clinical trial. For example:

- Medication Summary: Relevant for clinical trials related to drug administration but less so for trials related to medical devices. Medication information can provide insights into previous or ongoing pathologies. For instance, if a patient received chemotherapy, a history of cancer is likely, which is crucial information for assessing potential eligibility in most clinical trials.

The xShare core data element set is a comprehensive and valuable source of data for patient prescreening questionnaires, it is also a sufficient source of data as pre-screening only require high level data (demographics, pathologies, history…). The value of this BUC lies in the automatic filling of these prescreening questionnaires through EEHRxF health data sharing. This process assumes that patients have access to a PHR application, allowing them to access and complete their health data.

The PHR application would enable patients to share their data and self-nominate for clinical trials using the xShare Yellow Button. Additionally, the PHR app would allow patients to exercise their GDPR portability rights by informing them which data are used and enabling them to select, correct, or delete data to be shared. Patient control over health data sharing is a regulatory prerequisite and ensures respect for patient privacy.

Empowering patients to self-nominate for clinical trials is an effective way to improve patient recruitment. By becoming active participants in their healthcare journey, patients' motivation and follow-up success are likely to improve.

The user stories have highlighted 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 Button's data sharing functionality would benefit from a toggle feature, allowing patients to control their health data sharing.

Moreover, it is crucial for patients to receive feedback regarding their potential eligibility for a clinical trial. Therefore, communication between the prescreening tool and the PHR application is essential to provide results and information about compatible clinical trials and their locations. Location information is vital for patients to 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 the research team and clinical investigators, user stories have shown the need for functionalities that facilitate fluid information sharing to improve the process and save time. Data sharing must be efficient and relevant to avoid increasing screen failures, which would add to the investigative team's workload and diminish the benefits of this use case.

The final beneficiary of this use case is the sponsor, who will be involved in updating clinical trial registries to enhance recruitment efficiency in ongoing trials and reduce costs associated with the recruitment phase. This update involves real-time data sharing of current clinical trials and their locations, ensuring that patients are referred to trials with active recruitment rather than those that have concluded.

Whether for patients, the clinical investigation team or sponsors, the use of the xShare Yellow Button significantly enhances patient prescreening within the scope of clinical research. The EEHRxF data sharing introduces a new range of possibilities for prescreening and effectively addresses recruitment challenges.

The use case is executed to enhance patient/healthy volunteers' inclusion in clinical trials in order to answer to one of the biggest challenges in the conduct of a clinical trial, is the recruitment of the right number of patients within the allotted time. Benefits are for the patient/healthy volunteers to empower their health with their assessment in a clinical trial, for the Clinical investigator and the research team to be able to recruit the right number of patients and for both to advance clinical research. Sponsor/CRO will benefit from this process by reducing the time needed for the overall clinical realization phase.

The evaluation of the benefits and efficiency of this BUC can be performed by the direct assessment of the number of patients connecting to the app, referred to a clinical trial and included in a clinical trial.

However, the biggest challenges will be the deployment limitation with the hospital reluctancy to offer these services and lack of investigator champions within the institution. Moreover, the ability to transcribe protocol eligibility criteria in a machine-readable format and the continuous updated clinical trial registry (including recruitment status per investigation sites) will have to be taken into consideration as challenges.

3.1.3 BUC analysis: Support for data collection of a health study

The ambition of the third business use case is to leverage on one of the most time-consuming parts of the clinical realization for clinical research team: the data collection. This use case aims to accelerate eCRF filling by automating data entry directly from the patient health data of the IPS+R, EHR and PHR.

Data collection is the key for a robust and reliable analysis and consists of transcription of patient health data defined in the health study. The database for a clinical trial is defined by the set of CRF, known as eCRF when managed through IT systems, and consists of a structured dataset. By using an eCRF the research teams can efficiently organize patients' clinical information as required by the study, thereby facilitating the data collection and management process. This electronic approach also helps in reducing data entry errors and speeding up data processing, improving the reliability of the study results. The eCRF must contain all the data of interest as defined in the study design, according to the clinical trial methodology and pathology of interest. In compliance with current regulations, patient

anonymity must be maintained throughout the duration of the study. Therefore, a unique randomized pseudonymization code is assigned to each patient.

The eCRF forms are generally segmented by follow-up visit and by theme (i.e., eligibility criteria, adverse events, study exits, deviations).

To avoid potential data entry errors, it is advisable to set up instant consistency checks. These alerts and constraints can, for example, verify the consistency of numerical data or between multiple dates.

As the eCRF is a form filled with patients' health information and is a time-consuming task, it would benefit from automation under the patient's control. This BUC assumes that a mapping between the patient's health data contained in the IPS and future IPS+R is done with the eCRF. The overlap with the xShare IPS core data element set, detailed in section Appendix II: Overlap with IPS ,shows that all the data contained in the IPS would benefit from being mapped into a protocol eCRF.

This data set would be especially relevant for retrospective or observational studies based on RWD. Some data will be required for all protocols, such as demographic data like "age" or "birth date." These data contain the same information; commonly, the birth date is asked in the eCRF, allowing for an automatic calculation of age. Moreover, as the birth date could be identifying data, the information requested by the eCRF is only the month and year.

The "Allergies and Intolerance" section and "adverse event" data proposed in the IPS+R are very relevant to an alternative flow of this use case considering a prospective and interventional clinical trial, such as the evaluation of the efficacy and safety of a new treatment. Indeed, one of the most important parts of patient follow-up in a health study is ensuring their 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+R. Automating the SAE filling in the eCRF through EEHRxF in this use case would significantly improve patient safety in clinical trials.

Currently, some adverse events are not reported to the patient or the medical investigative team (if they occur between visits or are treated in another hospital). Some events are not reported by the investigative team either in the medical records or the eCRF (non-significant ones such as those

occurring between visits and resolving by the day of consultation), and some adverse events are reported with a delay. This use case will address these gaps in adverse event data reporting, thanks to the data sharing link offered by the xShare Button.

However, while all the data in the IPS+R are relevant to this BUC, the IPS+R alone may not be sufficient for complete eCRF data entry, as for example if the eCRF requires pseudonymized imaging. Moreover, considering an alternative but valuable flow with a prospective and/or interventional study, additional examinations (laboratory, imaging) or tests (questionnaires, pharmacokinetics) or questionnaires are often performed for the study's needs and purposes, requiring complementary data entry from the EHR and clinical trial specific source documents. Nevertheless, the partial automatic data entry proposed in this use case would greatly benefit the research team's daily work.

User stories have shown that the research team will benefit from automated data entry but will need to know the source of the data to perform quality control, especially in case of inconsistencies with other EHR data. The research team will also play a role in linking the patient with their pseudonymization number for the health study. Data sharing to the eCRF would be allowed by the patient through the PHR app containing the xShare Yellow Button, and they will need the ability to exercise their portability rights according to GDPR. Besides the advantages for the clinical investigation team, the sponsor will also benefit from this use case. There is often a delay between visits and data entry, and as the sponsor has access to the eCRF data, they use it as a clinical management tool to follow the patient's visits and clinical trial management. Automating the eCRF filling would allow the sponsor to access promptly data regarding the management of their studies and adapt the necessary supportive actions, including safety measures and critical risks management.

The position of the xShare Yellow Button in the scope of this business use case would have a major impact for the invitation and sponsor aspect all under the patient's control over their data.

The process offers several objectives, including streamlining data collection for both patients and the investigation team. By automating data entry, it reduces costs and effort associated with manual data collection.

However, the main challenges lie in the complex mapping of data sources to automatically complete the required eCRF. Furthermore, this task recurs for each CT since eCRFs can vary from one CT to another. For this task, the adoption of a common terminology and a consistent implementation of EEHRxF in the eCRF is crucial. However, it must ensure detailed specifications regarding data protection and data management, which could be included or specified in an ICF. In the frame of prospective studies, this would require authorization to collect data to fill in the eCRF from various IT systems (primarily EHRs) used in future encounters by different researchers and related centers. Additionally, it would authorize the use of data collected, specifically for a research study for normal patient care instead (transferring data from the eCRF to the EHR).

The application of this BUC should be opened to interventional prospective studies, however, this leads to another challenge. Indeed, in the scope of these studies' methodology, patients often undergo

several invasive exams after the ICF signature, even though the results may already be available through RWD/EHR/PHR. The interventional clinical research obliges to perform this process again. The world of clinical research has to evolve to recognize the validity of RWD, to ease the patient's quality of life; therefore, avoiding any unnecessary exams in the scope of the patient medical care. Moreover, the decrease in the number of procedures (e.g. medical visits) may also reinforce the willingness of patients to participate in CT.

3.1.4 Overall BUC analysis

For each of the business use case, the application of the EEHRxF to clinical research have demonstrated a strong interest, whether it is for European strategies regarding registries update and querying, or to empower patient with the control over their health data while easing the investigative teamwork and decreasing costs for medical and epidemiological research.

User stories suggested in the scope of the three business use cases present some convergence point. The common features that emerge can benefit the xShare Button integration and the EEHRxF implementation. This would allow the harmonization of the development of the functionalities.

Table 8 presents the merge of the user stories proposed for the 3 BUC and the scope related. 10 different themes emerge from the user stories.

The initial scope, relevant to both pre-screening and study support, pertains to the GDPR's portability right. The functionalities should incorporate a feature that allows patients to access, edit, modify, or delete their health data, granting them full control. Patient empowerment plays also a crucial role, particularly during pre-screening. By enabling patients to actively participate in clinical trials and health research and manage their involvement, the functionalities should treat patients as the trigger for the xShare Yellow Button. Lastly, information sharing is another vital functionality. Patients need clear and understandable information about potential clinical trials and health studies, whether they are in the feasibility process or pre-screening.

By automating research processes, we can enhance public health, benefiting both the general population and involving citizens and healthcare payers. The use cases will enable a broader segment of the population to actively participate in clinical trials and studies.

The research team plays a crucial role in three key areas: Prescreening, feasibility, and study support. By leveraging specific functionalities, they can transform their daily work practices. These enhancements lead to improved clinical research management by minimizing human errors, automating processes, and freeing up time for patient follow-up. Effective communication within the research team and with patients is also facilitated by these functionalities, which serve as a central hub for information exchange.

Moving on to the industry perspective, the latest user stories and functionalities are directly relevant. Study management benefits from precise information about active files and their locations, enabling optimal protocol proposals. Additionally, adherence to rigorous scientific methodology is ensured. The

sponsor's access to registry querying at EEHRxF further enhances efficiency. Economically, the sponsor gains a competitive edge through the reuse of EHR and PHR data.

Table 8 : Overview by category of the user stories

Scope	AS A (WHO)	I WANT (WHAT)	SO THAT (WHY)	BUCs* related
GDPR	Patient/ healthy volunteer	I want to exercise my GDPR rights (Access, Edit, modify, delete)	I have control over the data I want to share/I have Shared.	P, S
Patient empowerment	Patient/ healthy volunteer	Empower my control over my health data sharing to a clinical investigation team	My potential eligibility in a clinical trial can be assessed	P
Information sharing	Patient/ healthy volunteer	Receive information related to my compatibility to a CT and the CT major information description	I can evaluate my interest in participating in a CT and avoid any false hope	F, P
Public good	Citizen/health care payer	To contribute to clinical trial and drug development	I can advance public health research for the benefit of all	S, F
Time saving	Research team	Automate the flows applying to clinical research	I can save time	S,P
Quality	Research team	Improve the quality of clinical trial conduction at my site	I can avoid mistakes and have good reputation as a successful clinical site	F, S, P
Simplification	Research team	Share fluid patient information within my center	I can ease the burden the patient's recruitment in a clinical trial	P
Study management	Industry	Get precise and robust information regarding the future/ongoing investigation site	I can define the most adapted protocol to ensure the success of my study (eligibility criterion, design, sites)	F

Scope	AS A (WHO)	I WANT (WHAT)	SO THAT (WHY)	BUCs* related
			and the best follow-up of this site.	
Methodology	Industry	To be as precise as possible in my protocol conception	To maximize the scientific rigor of the study	F
Economy	Industry	To find wide-scale interest in reusing EHR data for clinical research	To have a strong market for my products	F

*F=Feasibility, P=Prescreening, S=Study support

The xShare core data element set has garnered significant interest and serves as the primary Health Information Domain (HID) for each of the three BUC. Specifically, the BUCs related to feasibility and study support benefit extensively from this comprehensive data set due to their inherent nature. It will be the basis for the specification of IPS+R, a proposal for a new health information domain under EEHRxF.

This Deliverable 5.2 also analyzes the application of the EEHRxF within the scope of clinical research, focusing on BUC. For the xShare project, Deliverable 3.1, as a part of WP3 “Patients’ Right to Data Portability: the case of continuity of care” focuses on BUCs for the applicability of EEHRxF HIDs in the context of continuity of care, building on previous projects. The aim is to describe and develop the xShare Button and EEHRxF, through entities called “adoption sites.” Eight adoption sites, representing eight different European countries, have proposed scenarios for the application of the xShare Yellow Button and the format. Some of these adoption sites have anticipated the application of the xShare Yellow Button for secondary use. Additional sites will be engaged through the open calls.

Greece’s Adoption Site: Implementation of the xShare service to give patients access, after identification, to EEHRxF-enabled EHR data in a structured format (CDA/FHIR). The service can be integrated into the MyHealth@EU services to ensure MVC compliance for cross-border use in the EU and will allow patients to share/donate their data for secondary use.

Cyprus’ Adoption Site: Development of a mobile application (PHR app) designed to provide citizens with access to their International Patient Summary (IPS) and the European Patient Summary (ePS). The application is designed to be user-friendly, ensuring that citizens can easily navigate and access their health summaries without technical difficulties. Although the use case does not mention secondary use, the structure of the tool suggested matches the requirements for the clinical research BUC.

Italy’s Adoption Site: Implementation of the “xShare Yellow Button” in a PHR (Monasterio App). By clicking on it, patients can download the structured content of the discharge summary in EEHRxF

format locally to their smartphone or computer. Patients will have the capability to share/donate data for secondary use.

Catalonia's Adoption Site: Introduction of a revised version of a tool called "Blue Button." This innovative tool is reshaping the European healthcare landscape by enabling citizens to securely access and download their clinical data in a structured XML format. The site is also working on the evolution and improvement of the xShare Yellow Button tool on the LMS portal/app, proposing a scenario where direct data donation for research is possible using intermediate tools/platforms.

Portugal's Adoption Site: Implementation of the xShare Yellow Button, allowing portability of the EHR from SEIS-RAM for patients from the Regional Health System in Madeira. The SEIS-RAM system communicates with previously developed digital solutions, such as the patient portal and the mobile app from SEIS-RAM, allowing patients to access this data upon registration and authentication. The xShare Yellow Button will be installed on the patient portal and the mobile app (PHR), allowing the EHR to be accessed, downloaded, and then shared. The Portuguese adoption site could be linked to the business use cases for patient prescreening and study support, where patients use a PHR app to share and donate their data in the context of participation in a clinical trial.

French Adoption Site: Accessibility for patients to structured health data using "Mon espace santé," and using the xShare Yellow Button service(s) to decide which data points are to be shared with clinical investigators. Data are available in CDA/FHIR formats. The patient uses the xShare Yellow Button service(s) to decide which data points are to be shared/donated with clinical investigators. The xShare Yellow Button service(s) will allow patient data conversion/upload/sharing in structured EEHRxF IPS and sending to the clinical investigator pre-screening tool. This is directly linked to the application of the BUC for patient prescreening with the PHR app being "Mon espace santé."

Each adoption site suggests the application of use cases considering the implementation of the xShare Yellow Button and the capability to share/donate their data through a PHR app, either at their organization level or within the European level. These use cases are complementary to the business use case for patient prescreening and study support, which are triggered by patients willing to share/donate their data for clinical research (before or after their inclusion in a clinical trial). The use cases suggested by the adoption sites focus on the preconditions needed for the application of the clinical research use case and are complementary.

The two other adoption sites (Irland and Danmark) do not consider secondary use and/or do not match with the BUC proposed in the scope of this Deliverable 5.2.

Health research encompasses a broad range of studies and various existing pathologies. For feasibility assessments, precision is crucial, necessitating queries across all available health data to ensure optimal study protocol design. Similarly, study support relies on the eCRF, which can be populated with health data based on the study methodology and target pathology. Therefore, a wealth of data is essential. While the entire data set is relevant for these use cases, the study support theme requires additional health data beyond what the IPS+R covers. For instance, specific clinical research examinations or structured data not included in the IPS+R may be necessary. In contrast, prescreening

focuses on generic data and utilizes only half of the data from the set. Remarkably, the xShare IPS+R core data element set is particularly valuable because it not only covers the required data but also provides additional information. Consequently, the entire prescreening process can rely solely on the data contained within this set, eliminating the need for supplementary health data. It is important to note that prescreening can also consider "non-health" factors, such as a patient's ability to understand questionnaires or their motivation regarding the number of visits. However, these aspects are addressed during the screening phase rather than at the prescreening level.

3.1.5 A History of EEHRxF

This section proposes a scenario for the application of the EEHRxF and the use of the xShare Yellow Button among the different BUCs; This is a story telling of a probable situation, one among many. The three BUCs are linked to each other in a chronological way. The first part of the story is based on the feasibility BUC, the second part on the patient's prescreening and the last part refers to the study support BUC.

Imagine a prospective clinical trial called "Study X" in the field of gastroenterology. Eligible patients must meet the following criteria:

- Age over 18 years old
- Present active ulcerative colitis
- Evidence of a lesion extending 20 cm above the anal verge
- Under treatment with biologics
- No history of cancer

The clinical trial designers aim to ensure that the protocol, especially the eligibility criteria, aligns with the reality of ulcerative colitis (UC) patients. They have the opportunity to generate federated queries on registries containing the health data at the EEHRxF for 20 hospitals among the country. The RWD from these registries reveal the distribution of UC patients across different hospitals: 3 hospitals account for 50% of the UC population. Consequently, the project team prioritizes collaboration with these hospitals to maximize patient recruitment. Interestingly, the query results highlight another crucial point: 35% of patients present lesions extending 20 cm above the anal verge. However, this proportion significantly increases to 75% when the lesion extends only above 15 cm. After thorough discussions with the scientific committee and the project team, considering risk-benefit analysis and maintaining scientific rigor, the team decides to adapt the criterion. They revised the limit for the lesion to 15 cm above the anal verge: The protocol feasibility is validated, and the investigation sites are selected regarding their active file.

The project team can launch the clinical trial and each of the investigative sites are open to enroll patients in the study x.

At home, Patient Z, who suffers from UC, faces challenges in adhering to their biological treatment. Eager to take control of their health, Patient Z expresses interest in participating in a clinical trial to improve their condition. Fortunately, they have access to a PHR app, which allows them to track ongoing treatments, monitor pathologies, and access lab results. Within the app, Patient Z has access to a "Clinical Studies" section that enables them to assess their eligibility for ongoing trials—an opportunity to actively engage in their medical follow-up. By enabling data sharing through the xShare

Yellow Button, Patient Z receives a notification about potential compatibility with clinical studies. Based on the shared data, Patient Z has an 80% chance of being compatible with Study X, currently underway in three hospitals across their country. Intrigued by the prospect, Patient Z expresses interest in participating at Hospital B, conveniently located near their home, and the system promptly sends a compatibility notification to the study site. Hospital B, upon receiving the compatibility notification for Study X, sends additional questions to the patient's through PHR app. The purpose is to share crucial information about the study. During the study duration, three additional colonoscopies, beyond the current practice, are expected. Given that this procedure is highly invasive, Patient Z must carefully weigh the pros and cons of their participation. After receiving additional information from Hospital B, Patient Z confirms their potential interest in participating in Study X. An on-site visit is then planned to assess Patient Z's full eligibility.

The patient Z signs the ICF and is included in the study X in the hospital B.

In the context of this study, the sponsor utilizes an eCRF compatible with EEHRxF to collect a portion of the data required for the clinical trial. The eCRF also offers the possibility to link data from the IPS+R (including history, lab results) to the eCRF. The research team assists patient Z in establishing the connection between Study X and data sharing from the PHR by entering the subject's ID number in the app. During the inclusion visit, data are automatically populated in the eCRF through data mapping within EEHRxF, establishing the link between the patient and the study. In parallel with the data sharing from the PHR app, data can also come from the EHR and complete the eCRF. Whenever new information relevant to the eCRF becomes available in the PHR and/or the EHR, updates are made to the eCRF. Unfortunately, during their participation, Patient Z experienced an increase in their transaminases beyond the normal range, which is considered an adverse event within the scope of Study X. Health data related to this event, available in the IPS+R, are automatically entered into the eCRF. Additionally, the on-site research team accesses the eCRF to complete data not present in the EHR, such as specific Study X questionnaires, and to validate data automatically filled in by the system.

The patient Z is followed in the study X by the investigation team of hospital B until the end of their participation.

This is just one story among a multitude of applications. The EEHRxF has the potential to significantly transform the way clinical research is conducted for all stakeholders involved.

4. Conclusion

This deliverable aims to analyze various business use cases related to clinical research within the scope of the xShare project, leveraging real-world EHR data. The objective was to examine clinical research methodologies and workflows that utilize RWD across key use cases, including protocol feasibility assessment, site selection, patient pre-screening, consent management, data transfer, core eCRF completion, and innovative trial design. The use case analysis demonstrated the value of EHR data at different levels of clinical research, specifically feasibility, patient pre-screening, and study support. Leveraging the EEHRxF for data sharing—whether through direct patient interaction or querying registries—becomes crucial. By promoting EU-wide health data interoperability and enhancing patient care and clinical research, the EEHRxF goes beyond mere format recommendations. It enables clinical research to reach new heights by streamlining protocol decisions and automating processes.

This deliverable 5.2 (D5.2), which has demonstrated the relevance of the application of the EEHRxF and the xShare Yellow Button in the field of clinical research, is part of a broader context within Work Package 5, titled “European EHRxF in Clinical Research: Core-Set and IPS+R.” This work package is divided into four interlinked tasks. Deliverable 5.1 (D5.1) aimed to harmonize data elements and was produced upstream of D5.2, which utilized the work from D5.1 to establish the relevance of these data elements within the scope of clinical trials. The outcomes from these two deliverables will form the basis for task 5.3, which will focus on harmonizing data element requirements to propose the IPS+R. The BUCs functional and technical specifications will be elaborated in task 5.4 and be submitted to an open call for partners willing to develop demonstrators. This open call also aims to leverage GDPR portability to enable patients to access and contribute to data research, thereby evaluating the impact of the xShare Yellow Button position. The BUCs related to pre-screening and feasibility will find the greatest value within the scope of this open call and will benefit from being demonstrated.

In the scope of this D5.2, significant attention has been given to applying GDPR’s portability clause (art. 20 GDPR) to mobile PHR and trial solutions. Specifically, the use cases of pre-screening and study support empower patients as the controllers of their own data. Through their PHR app, patients have exclusive control over sharing health data using the xShare Yellow Button. Additionally, patients can access all relevant information and exercise their portability rights. The PHR app plays a crucial role in empowering patients to take charge of their data.

The deliverable analysis involved conducting desk research to gather relevant data sets, identify recurring data elements, and comparing them with the IPS+R. Through this process, a significant overlap between the IPS+R and all the business use cases has been demonstrated. The IPS+R demonstrated its value across various scenarios, including protocol feasibility assessment, site selection, patient pre-screening, consent management, data transfer, core eCRF completion, and innovative study design. However, to effectively conduct these business use cases, a harmonized core data element set within the EEHRxF becomes essential. This harmonization ensures consistency and facilitates seamless data sharing across different contexts.

The overall goal is to reuse structured patient data for clinical research while assessing its impact on efficiency and individual data control. This deliverable demonstrated an efficiency improvement by leveraging existing health data: researchers can streamline processes such as patient recruitment, protocol design, and data collection and faster access to relevant information to reduce administrative overhead and accelerate research timelines. Researchers can also make informed decisions based on

historical data, leading to more efficient study execution and reducing the risk of patients' withdrawals. Another benefit would be the enhancement of individuals over their health data control. Indeed, patients become active participants in clinical research by granting consent for data sharing. Patient empowerment through control over their data ensures transparency and builds trust, while allowing reuse of structured data from EHR. This ensures consistency and accuracy for researchers that benefit from comprehensive, standardized data, while reducing errors and enhancing study reliability. Moreover, avoiding redundant data collection minimizes costs associated with duplicate efforts and efficient data reuse optimizes resource allocation and budget utilization. There are still some challenges such as:

- Privacy concerns: Balancing data sharing with privacy protection remains critical.
- Data interoperability: Ensuring seamless exchange across different systems and institutions.
- Ethical considerations: Safeguarding patient rights while advancing research.

Following this deliverable, it is necessary to consider the great value of the EEHRxF application to clinical research, particularly focusing on the implementation of the BUCs described by the working group. The BUCs related to prescreening and study support will align with the open call under the EUCROF code of conduct in ensuring the demonstration of their feasibility. Additionally, the BUC related to study feasibility, as a continuation of an existing use case, could be established but will require coordination among member states to facilitate its implementation.

In summary, structured patient data reuse can revolutionize clinical research, promoting efficiency, individual empowerment, and data-driven insights. However, careful implementation and ethical handling are essential. Only agreement and harmonization between the actors and organizations as the initiative of the xShare project, will allow to resolve the challenges.

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6. Appendix I: BUC global listing

6.1 Patient pre-screening in clinical trial through healthcare professional pre-screening tool

In this use case, the xShare Button is activate by the patient to share data from IPS+R to a pre-screening software. This pre-screening tool is used by HCPs at site, which consists in answering a short medical questionnaire filtering automatically the right clinical trials according to the patient profile. The workflow with the xShare Button would start with the patient sharing data thanks to the xShare Button allowing the patient data uploaded into the prescreening tool. Then, according to the available data, answers to the medical questionnaire are automatically fulfilled and the physician reviews the answers provided, and answers the questions left without answer. The prescreening tool indicates the studies for which the patient is potentially eligible for and the physician selects one or more studies for which he wants to refer the patient. A notification is sent to the study team to facilitate the coordination onsite for future patient inclusion.

6.2 Patient self-nomination as possibly eligible for a trial

In this use case, the patient can download their summary via the xShare Button, especially if this is the IPS+R. An app on their smart device scans online (computable) trial eligibility criteria in their country and offers the patient a suggestion for a trial that is openly recruiting and for which they may be eligible. It offers the patient a contact channel (email, phone etc.) if the patient wishes to enquire about enrollment.

6.3 Protocol feasibility via a repository of IPS+R summaries, e.g. at hospital, regional or national level

This BUC assumes that the xShare IPS+R stimulates greater investments in having good quality summaries, implementing the necessary EHR system interoperability and investing in clinical data repositories with populations of such summaries. These might be intended for patient care (primary use) but could easily be queried anonymously to implement the original EHR4CR use case of profiling patient numbers against candidate eligibility criteria, to establish the feasibility of the study and to refine the criteria to maximize the chances of good recruitment. Federated querying would enable the scalability of the insights.

6.4 Targeted patient recruitment via a repository of IPS+R summaries, e.g. at hospital, regional or national level

This BUC also utilizes one or more repositories of IPS+R summaries. It assumes that a final recruitment query on a study could be executed by authorized persons to extract a candidate list of patients who might be eligible. This list might feed into an electronic pre-screening or be used as a direct invitation list to contact patients and invite them to consider participation.

6.5 Clinical Study support – whole scenario (side effect reporting)

A clinical study is defined to assess the prevalence of reported side effects and their association with disease and drug characteristics in patients with chronic hypertension.
Inclusion criteria are: 1) age > 18 years, 2) history of hypertension and therapy with anti-hypertensive drugs, 3) ability to provide informed consent.
At enrolment, patients will be asked to fill a study questionnaire focused on the perceived side effects of antihypertensive medications on an application. The Patient's app enables the xShare Button when all the required information is ready, and clicking on the xShare Button the patient create the research dataset, in the EEHRxF format, or IPS if applicable and send it to the research center that is leading the investigation, applying anonymization/pseudonymization/identified-patient criteria as defined in the clinical study.
Main Pre-condition: granted consent from the patient to collect data in the patient's app, clinical study approved by the reference ethical committee, candidate patient selected with the anonymous application of the selection criteria with no data shared with research center, patient informed consent document describes P.I. and research sponsors, benefits, length of the study, data management.
Main Post-Condition: without explicit permission data can be used only for the clinical protocol granted by the patient with his/her consent. Another protocol requires another explicit permission.

6.6 Longitudinal cohort tracking

In this BUC, an HCP agreed to maintain a list of patients with a particular disease and uses the IPS+R as a data set to maintain a pseudonymised data warehouse with this data (or can generate it just in time on demand). This provides a permanently available longitudinal natural history study and virtual study recruitment pool.

6.7 Clinical Study definition

After the authorization granted for the execution of a clinical study (ethical committee), it is needed to configure the different clinical IT systems, corresponding to the different source of data, to select the right candidates having the information required, considering also retrospective information, and having a match on selection criteria.
This can be expressed in a processable FHIR bundle, describing the eCRF in a structured format, and applicable as a filter or data input guide usable in EHR, PHR systems or IPS+R repositories
The candidate list represents the basis for further processing, or actions in case of patient's consent submission for each candidate (when required).

6.8 Clinical Study follow-ups

In this use case, a clinical study requires the periodic compilation of a questionnaire (i.e. every week or every 6 months, etc.). In a specific section of a patient App/portal there is a reminder to do it, and a link that forwards to the questionnaire. The patient compiles the questionnaire and at the end press on the xShare Button to send the questionnaire (anonymized/pseudonymized according to the study design) to the reference research center (or Dataspace/repository). The questionnaire can be represented in EEHRxF using FHIR resources (Questionnaire/ QuestionnaireResponse) or embedded in IPS+R.

6.9 Site feasibility guided by the xShare Button

This BUC also utilizes one or more repositories of IPS+R summaries. This BUC aims to use the xShare Button to assess site feasibility. Site selection is a major challenge to ensure the success and relevance of a clinical study. Indeed, recruiting an adequate number of subjects is the most challenging part of conducting a clinical trial for data analysis. Sites must be selected in accordance with their patients, and the number of sites participating in the clinical trial must be determined based on each site's recruitment capacity. Data shared from IPS+R through the xShare Button will provide crucial information to qualify each center's population.

In this use case, patients share their data with the xShare Button. Data is analyzed in several dashboards and can provide an overview of the types of patients being monitored in an area: sites can be selected based on precise data regarding the patients being monitored. Then Sponsor/CRO can gain access to dashboards and identify the relevant sites for their clinical trial and sites can gain access to dashboard and identify which clinical trial are the most compliant with their practice and patient populations.

6.10 eCRF Filling Process through the xShare Button

The patient included in a clinical trial shares his/her data using the xShare Button to complete the eCRF. The patient is registered as being part of the clinical trial, which establishes the data link needed from the IPS+R to the eCRF. A mapping is performed from core data elements to the eCRF and the patient can share data related to exams performed between visits, such as: in-town biology, concomitant treatments, and self-questionnaires. The patient can share data to monitor ongoing adverse events and actions taken (treatment, other visits to health providers, etc.). The patient can share data from medical devices linked to an app using the xShare Button

7. Appendix II: Overlap with IPS

Table 9 : BUC's Data overlap with the xShare coredata element set

Data requirement			IPS Category	Data Element
Feasibility	**Prescreening**	**Study support**		
Not Required	Not Required	Required	Subject	Study Identifier
Not Required	Not Required	Required	Subject	Study Site Identifier
Not Required	Not Required	Required	Subject	Research Subject Identifier for the study
Not Required	Not Required	Required	Subject	Research Unique Subject Identifier
Not Required	Not Required	Required	Subject	Research Study Identifier
Required	Required	Required	Subject	Age
Required	Required	Required	Subject	Age Units
Optional	Required	Required	Subject	Demographics Collection Date
Required	Required	Required	Subject	Sex (Administrative/clinical use?)
Required	Required	Required	Subject	Birth Date
Required	Not Required	Optional	Subject	Deceased Date
Required	Not Required	Optional	Subject	Deceased Flag
Required	Not Required	Required	Subject	Subject Characteristic Collection Date
Required	Not Required	Recommended	Subject	Subject Characteristic
Required	Not Required	Recommended	Subject	Subject Characteristic Finding Value
Required	Not Required	Recommended	Subject	Subject Characteristic Finding Value Units
Required	Required	Required	Problem List	Medical History Collection Date
Required	Required	Required	Problem List	Medical History Reported Term
Required	Required	Required	Problem List	Medical History Event Start Date
Required	Optional	Optional	Problem List	Medical History Event End Date
Required	Required	Required	Medication Summary	Medication
Required	Required	Required	Medication Summary	Medication Dose
Required	Required	Optional	Medication Summary	Medication Dose Text (for range doses)
Required	Required	Required	Medication Summary	Medication Dose Unit
Required	Required	Required	Medication Summary	Medication Indication
Required	Optional	Required	Medication Summary	Medication Dose Form
Required	Required	Required	Medication Summary	Medication Dose Frequency
Required	Required	Required	Medication Summary	Medication Route of Administration
Required	Required	Required	Medication Summary	Medication Start Date

Data requirement			IPS Category	Data Element
Feasibility	Prescreening	Study support		
Required	Required	Required	Medication Summary	Medication Ongoing
Required	Required	Required	Medication Summary	Medication End Date
Required	Required	Required	History of Procedures	Procedure
Required	Required	Required	/	Procedure Start Date
Required	Required	Required	History of Procedures	Procedure Indication
Required	Required	Required	/	Procedure Ongoing
Required	Required	Required	History of Procedures	Procedure End Date
Required	Required	Recommended	Pregnancy Status, Hx & Summary	Reproductive Finding Name
Required	Optional	Recommended	Pregnancy Status, Hx & Summary	Reproductive Finding Result Value
Required	Optional	Recommended	Pregnancy Status, Hx & Summary	Reproductive Finding Result Value Units
Required	Optional	Recommended	Pregnancy Status, Hx & Summary	Reproductive Finding Date
Required	Required	Required	Vital Signs	Vital Signs Test Name
Required	Required	Required	Vital Signs	Vital Signs Test Date
Required	Not Required	Required	Vital Signs	Vital Signs Test Time
Required	Required	Required	Vital Signs	Vital Signs Result Value
Required	Required	Required	Vital Signs	Vital Signs Result Value Units
Required	Required	Required	Diagnostic Results	Body System Diagnostic Test Date
Required	Required	Required	Diagnostic Results	Body System Diagnostic Test Name
Required	Required	Required	Diagnostic Results	Body System Diagnostic Test Result Value
Required	Required	Required	Diagnostic Results	Body System Diagnostic Test Result Value Unit
Required	Required	Required	Diagnostic Results	Body System Diagnostic Test Anatomical Location
Required	Required	Required	Diagnostic Results	Laboratory Specimen Collection Date
Required	Required	Required	Diagnostic Results	Laboratory Specimen Collection Time
Required	Required	Required	Diagnostic Results	Laboratory Specimen Type
Required	Required	Optional	Diagnostic Results	Laboratory Fasting Status
Required	Required	Required	Diagnostic Results	Laboratory Test Name
Required	Required	Required	Diagnostic Results	Laboratory Result Value

Data requirement			IPS Category	Data Element
Feasibility	**Prescreening**	**Study support**		
Required	Required	Required	Diagnostic Results	Laboratory Result Value Units
Required	Not Required	Not Required	Diagnostic Results	Laboratory Specimen ID
Required	Optional	Recommended	Diagnostic Results	Laboratory Method of Test
Required	Not Required	Recommended	Diagnostic Results	Lab Ref Range Lower Limit in Orig Unit
Required	Not Required	Recommended	Diagnostic Results	Lab Ref Range Upper Limit in Orig Unit
Required	Recommended	Required	Diagnostic Results	Laboratory Reference Indicator
Required	Recommended	Required	Diagnostic Results	Microbiology Specimen Collection Date
Required	Recommended	Required	Diagnostic Results	Microbiology Specimen Collection Time
Required	Required	Required	Diagnostic Results	Microbiology Test
Required	Required	Required	Diagnostic Results	Microbiology Test Result Value
Required	Required	Required	Diagnostic Results	Microbiology Test Result Value Units
Required	Recommended	Required	Diagnostic Results	Microbiology Specimen Type
Required	Recommended	Recommended	Diagnostic Results	Microbiology Test Method
Required	Not Required	Not Required	Diagnostic Results	Microbiology Reference ID
Required	Required	Recommended	Diagnostic Results	Microbiology Specimen Collection Location
Required	Required	Recommended	Diagnostic Results	Microbiology Examination Test Detail
Not Required	Required	Required	Social History	Substance Use Reported Name
Not Required	Required	Required	Social History	Substance Usage
Not Required	Not Required	Required	Social History	Substance Dose Description
Not Required	Not Required	Optional	Social History	Substance Dose (nontext)
Not Required	Not Required	Required	Social History	Substance Dose Units
Not Required	Not Required	Required	Social History	Substance Use Frequency
Not Required	Not Required	Required	Social History	Substance Use Start Date
Not Required	Not Required	Required	Social History	Substance Use End Date
Not Required	Not Required	Optional	Social History	Substance Use Duration
Not Required	Not Required	Optional	Social History	Substance Use Duration Unit
Optional	Not Required	Required	/	Healthcare Encounter
Optional	Not Required	Required	/	Healthcare Encounter Start Date
Optional	Not Required	Required	/	Healthcare Encounter End Date
Optional	Not Required	Required	/	Reason for Healthcare Encounter

Data requirement			IPS Category	Data Element
Feasibility	Prescreening	Study support		
Required	Required	Required	Allergies and Intolerances	Adverse Event
Required	Not Required	Required	Allergies and Intolerances	Adverse Event Start Date
Required	Not Required	Required	Allergies and Intolerances	Adverse Event Start Time
Required	Not Required	Required	Allergies and Intolerances	Ongoing Adverse Event
Required	Not Required	Required	Allergies and Intolerances	Adverse Event End Date
Required	Not Required	Required	Allergies and Intolerances	End Time of Adverse Event
Required	Not Required	Required	Allergies and Intolerances	Adverse Event Severity
Required	Not Required	Required	Allergies and Intolerances	Adverse Event Toxicity Grade
Required	Not Required	Required	Allergies and Intolerances	Adverse Event Serious Event
Required	Not Required	Recommended	Allergies and Intolerances	Adverse Event Results in Death
Required	Not Required	Required	Allergies and Intolerances	Adverse Event is Life Threatening
Required	Not Required	Required	Allergies and Intolerances	AE Requires or Prolongs Hospitalization
Optional	Not Required	Required	Allergies and Intolerances	AE Persist or Significative Disability/Incapacity
Required	Not Required	Required	Allergies and Intolerances	AE Congenital Anomaly or Birth Defect
Optional	Not Required	Required	Allergies and Intolerances	AE Needs Intervention to Prevent Impairment
Required	Not Required	Required	Allergies and Intolerances	AE Other Medically Important Serious Event
Required	Not Required	Required	Allergies and Intolerances	AE Involves Cancer
Required	Not Required	Required	Allergies and Intolerances	AE Causality
Optional	Not Required	Required	Allergies and Intolerances	Actions Taken with Device
Required	Not Required	Required	Allergies and Intolerances	Any Other Actions Taken
Required	Not Required	Required	Allergies and Intolerances	Outcome of Adverse Event