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**Survey by ECRIN about national registries for observational studies and sharing of individual participant data**

**Report**

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**Introduction**

The WHO (World Health Organization) Registry Network provides prospective trial registries with a forum to exchange information and work together to establish best practice for clinical trial registration. The main aim of the WHO ICTRP (International Clinical Trials Registry Platform) is to facilitate the prospective registration of the [WHO Trial Registration Data Set](https://www.who.int/clinical-trials-registry-platform/network/who-data-set) on all clinical trials, and the public accessibility of that information. The WHO ICTRP covers 17 primary registries (<https://www.who.int/clinical-trials-registry-platform/network/primary-registries>) (table 1). It is also possible to search other registries such as [clinicaltrials.gov](https://clinicaltrials.gov/) (<https://classic.clinicaltrials.gov/>).

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| **Primary registry** |
| Australian New Zealand Clinical Trials Registry (ANZCTR) |
| Brazilian Clinical Trials Registry (ReBec) |
| Chinese Clinical Trial Registry (ChiCTR) |
| Clinical Research Information Service (CRiS), Republic of Korea |
| Clinical Trials Registry - India (CTRI) |
| Cuban Public Registry of Clinical Trials(RPCEC) |
| EU Clinical Trials Register (EU-CTR)\* |
| German Clinical Trials Register (DRKS) |
| Iranian Registry of Clinical Trials (IRCT) |
| International Standard Randomised Controlled Trial Number (ISRCTN) |
| International Traditional Medicine Clinical Trial Registry (ITMCTR) |
| Japan Registry of Clinical Trials (jRCT) |
| Lebanese Clinical Trials Registry (LBCTR) |
| Thai Clinical Trials Registry (TCTR) |
| Pan African Clinical Trial Registry (PACTR) |
| Peruvian Clinical Trial Registry (REPEC) |
| Sri Lanka Clinical Trials Registry (SLCTR) |

**Table 1: Primary registries covered by the WHO ICTRP** \*As of 31 January 2023 change to the Clinical Trials Information System (CTIS)

Registration of clinical trials has continuously increased over recent years. Through its clinical research Metadata Repository (crMDR) ECRIN (European Clinical Research Infrastructure Network) performed an analysis of the number of registered trials, obtaining data directly from ClinicalTrials.gov, ISRCTN (International Standard Randomised Controlled Trial Number), EU CTR (EU Clinical Trials Register), and the other 15 registries via WHO ICTRP as well as the distribution of interventional and observational studies (February 2024).

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**Figure 1: Number of trials reported in the crMDR** (by study start year)

From the studies included in the crMDR analysis around 80% are interventional and 20% observational (Figure 2). Considering that many more observational studies have been performed, this indicates substantial underreporting of observational studies in existing trial registries. This and the narrow focus of the European Medicines Agency (EMA) systems (only clinical trials of investigational medicinal products (CTIMPs), medical devices, and post-marketing trials are included) have led to activities, building up national registries for observational studies in individual countries (e.g. France, Germany) (1).

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**Figure 2: Proportion of interventional/observational studies in the crMDR** (by study start year)To assess the status of national developments with respect to registries for observational clinical studies we have performed a survey within ECRIN. Additionally, this survey was targeted at the needs and requirements for data sharing of individual participant data (IPD) from clinical trials/clinical studies.

**Methods:**

The survey was targeted at the 12 member and 1 observer countries of ECRIN (Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Norway, Poland, Portugal, Slovakia, Spain, Switzerland).

A questionnaire was sent to the Network Committee members of ECRIN, representing the National Scientific Networks of Clinical Trial Units (CTUs), in October 2023. The following questions were included in the questionnaire:

* Is there a national registry for health studies already in place in your country?
* Is there a national repository in place, where IPD from clinical studies/clinical trials can be stored and shared for secondary use?
* Is there an interest in your national scientific network of CTUs to use the repository developed by ECRIN in an EU-funded project (clinical research Data Sharing Repository) for storing and sharing IPD from clinical trials/clinical studies?

The analysis presented in this report is restricted to national activities covering all types of clinical studies/trials, disease-specific or regional activities were not considered.

**Results**

8 countries participated in the survey (France, Germany, Greece, Ireland, Italy, Portugal, Spain, Switzerland). From the information received, 6 out of 8 countries reported national activities with respect to registries for observational or health studies. In one country (Greece) the activities are restricted to clinical trials (phase 1-4).

The French **FRESH Portal for Health Studies**, aims to become the national reference portal for all individual studies in the field of health with an open science approach. It is intended for health researchers (professionals who conduct scientific investigations and studies related to various aspects of health and health care) without restrictions institutions and funding parties. It covers all studies with individual health data, including clinical research, humanities and social sciences (<https://iresp.net/en/our-areas-of-activity/health-studies-portal/>). In addition, there is a register under development by the French Ministry of Health called **ECLAIRE** (<https://sante.gouv.fr/IMG/pdf/base-nationale-des-essais-cliniques-rapport-de-consultation-janvier-2023.pdf>). It is a platform (open API) which provides exhaustive data on clinical trials submitted to the French authorities. This register collects the data that sponsors provide during the submission process from RIPH2G (Recherches Impliquant la Personne Humaine 2ème Génération) and CTIS (**Clinical Trials** Information System). Data are available in French. The objective of this register is to foster recruitment in clinical trials by giving access to ongoing trials to sponsors, clinicians and patients.

In the context of the National Research Data Infrastructure for Personal Health Data (NFDI4Health) activity, Germany has implemented the German Central Health Study Hub. The NFDI4Health Study Hub is an inventory of German studies covering structured health data from administrative databases, clinical trials including vaccination studies, primary care, epidemiological studies, and public health surveillance. The aim is to enable the findability of studies and access to structured health data to improve the management of public health data. Unlike other initiatives, the NFDI4Health Study Hub will focus not only on clinical research but also on studies relating to the consequences of the pandemic on public health, such as utilisation of healthcare services, quality of life and the effects of social isolation. Furthermore, the hub provides access to instruments like (sample) questionnaires and information down to the variable level. Currently, 1561 studies, instruments and other documents are available (<https://csh.nfdi4health.de/search/Study>). Apart from the German Central Health Study Hub, there is the DRKS (German Registry of Clinical Studies) in place, one of the primary WHO ICTRP registries. Both registries are open to all kinds of clinical and observational/epidemiological studies. DRKS is mainly focused on clinical trials, whereas the German Health Study Hub has specific items for observational, epidemiological and public health studies.

In Greece, only prospective clinical trials (phase 1 to 4) that have been submitted to the National Organisation for Medicines are registered. Here, only lists of clinical studies for a given year can be accessed (<https://www.eof.gr/web/guest/ct-list>).

In Italy, the Registry for Observational Studies (RSO) has been established at national level. It is available since 31 January 2023 (<https://www.aifa.gov.it/en/registro-studi-osservazionali>). The RSO represents the management tool for non-interventional studies conducted on the national territory and is complementary to the National Observatory on Clinical Trials (OsSC), which covers and manages the authorisation process for clinical trials (phase 1 to 4) conducted in Italy. Access to the OsSC is restricted to sponsors and Contract Research Organizations (CROs) who can see only their studies, no other external users are allowed.   
  
In Portugal, a National Registry of Clinical Studies (RNEC) has been implemented (<https://www.rnec.pt/>). It covers all clinical studies in Portugal that involve human beings, namely, clinical trials and other studies of a clinical nature involving investigational products, medicines, medical devices, and cosmetic products. The registry combines a free access area, enabling the publication of the clinical trial and other relevant information, and a restricted access area (FrontOffice), permitting the sponsor to manage the clinical trial development through the submission of notifications, substantial amendments, end of trials notifications, withdrawals and serious adverse events. Furthermore, the sponsor or applicant is able to monitor the current state of each notification/submission.

In Spain, clinical trials are registered through **ReEC** (**Registro Español de Estudios Clínicos, Spanish Register of Clinical Studies**) ([https://reec.aemps.es/reec/public/web.html#](https://reec.aemps.es/reec/public/web.html)) and observational studies with drugs are registered through **GESTO-ReEC** (**Registro de Estudios Observacionales con Medicamento ya autorizados, Register of Observational Studies with already authorised** **Medicines)** ([https://gesto.aemps.es/gesto/faces/index.xhtml](https://emea01.safelinks.protection.outlook.com/?url=https%3A%2F%2Fgesto.aemps.es%2Fgesto%2Ffaces%2Findex.xhtml&data=05|02||a3b95df2917141045b6508dc32f3f5b3|84df9e7fe9f640afb435aaaaaaaaaaaa|1|0|638441270608904571|Unknown|TWFpbGZsb3d8eyJWIjoiMC4wLjAwMDAiLCJQIjoiV2luMzIiLCJBTiI6Ik1haWwiLCJXVCI6Mn0%3D|0|||&sdata=IWAq1s7ekE%2FiDg3mR9rZ3iI8tsbD1Hy8bAhLuKuBov8%3D&reserved=0)).

Finally, in Switzerland, the **SNCTP (Swiss National Clinical Trials Portal)** is the portal where clinical trials in Switzerland are published. It contains data from two sources: from BASEC (Business Administration System for Ethics Committees), the national platform for submitting applications for research projects to ethics committees, and from the ICTRP (the WHO International Clinical Trials Registry Platform), which covers the 17 primary registries worldwide. The ICTRP clinical trials shown on the SNCTP are limited to those conducted in Switzerland; there is also an option to display trials conducted in one of Switzerland's neighbouring countries.

Funders of study registries and access conditions to the registries are summarised in table 2. The registries are usually funded by health or research ministries or national agencies. The access is usually open and free of charge.

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| --- | --- | --- | --- | --- |
| **Country** | **National registry** | **Funder** | **Access** | **Comments** |
| France | FRESH (Portal for Health Studies) | Research Ministry | Open, free of charge | There is a register for oncological clinical trials, INCA |
|  | ECLAIRE | Health Ministry | Open, free of charge |  |
| Germany | DRKS (German Registry of Clinical Studies) | Health Ministry | Open, free of charge | DRKS is a primary WHO registry |
| German Central Health Study Hub | NFDI4Health | Open, free of charge | There are several databases of medical registries |
| Greece | Prospective clinical trials submitted to the National Organisation for Medicines | Greek National Organisation for Medicines | Free of charge | List of clinical studies for a given year (pdf) |
| Ireland | Not planned | - | - | Database of ongoing studies & trials (mirror of WHO) |
| Italy | Registry of Observational Studies (RSO) | Government | Sponsors, free of charge | Limited access for external users after registration |
|  | Registry of Clinical Studies/Trials (IRCCS) | Health Ministry/region | Open, free of charge |  |
| Portugal | National Registry of Clinical Studies (RNEC) | Health Ministry | Free access area, restricted access area for sponsors | Fees for clinical trial initial submission and substantial amendments |
| Spain | ReEC (Registro Español de Ensayos Clínicos, Spanish Register of Clinical Trials) | AEMPS (Agencia Española del Medicamento y Productos Sanitarios) Spanish Agency for Medicines and Health Products). | Open, free of charge | Primary source for clinical trials on medicinal products |
| GESTO-ReEC (Registro Español de Estudios Observacionales con Medicamento, Spanish Register of Observational Studies with Medicines) | AEMPS (Agencia Española del Medicamento y Productos Sanitarios) Spanish Agency for Medicines and Health Products). | Open, free of charge |  |
| Switzerland | SNCTP (Swiss National Clinical Trials Portal) | State | Open, free of charge |  |

**Table 2: Summary of the feedback to the question « Is there a national registry for health studies already in place in your country? »**

Question 2 was dedicated to the availability of national repositories, where IPD from clinical studies/clinical trials can be stored and shared for secondary use.

Here only France reported about a Multidisciplinary repository for all kinds of research data (*Recherche.data.gouv).* **Recherche Data Gouv,** funded by the French government,aims to become a European Open Science Cloud (EOSC) service, offering access to shared and open research data to support reuse. For 5 countries no such activity is planned and in Germany only individual datasets are available (e.g., Napkon public dataset, NAKO national cohort, module clinical trials of Medical Informatics Initiative). In Spain, a repository initiative is under way but related to omics data in medicine not clinical trials.

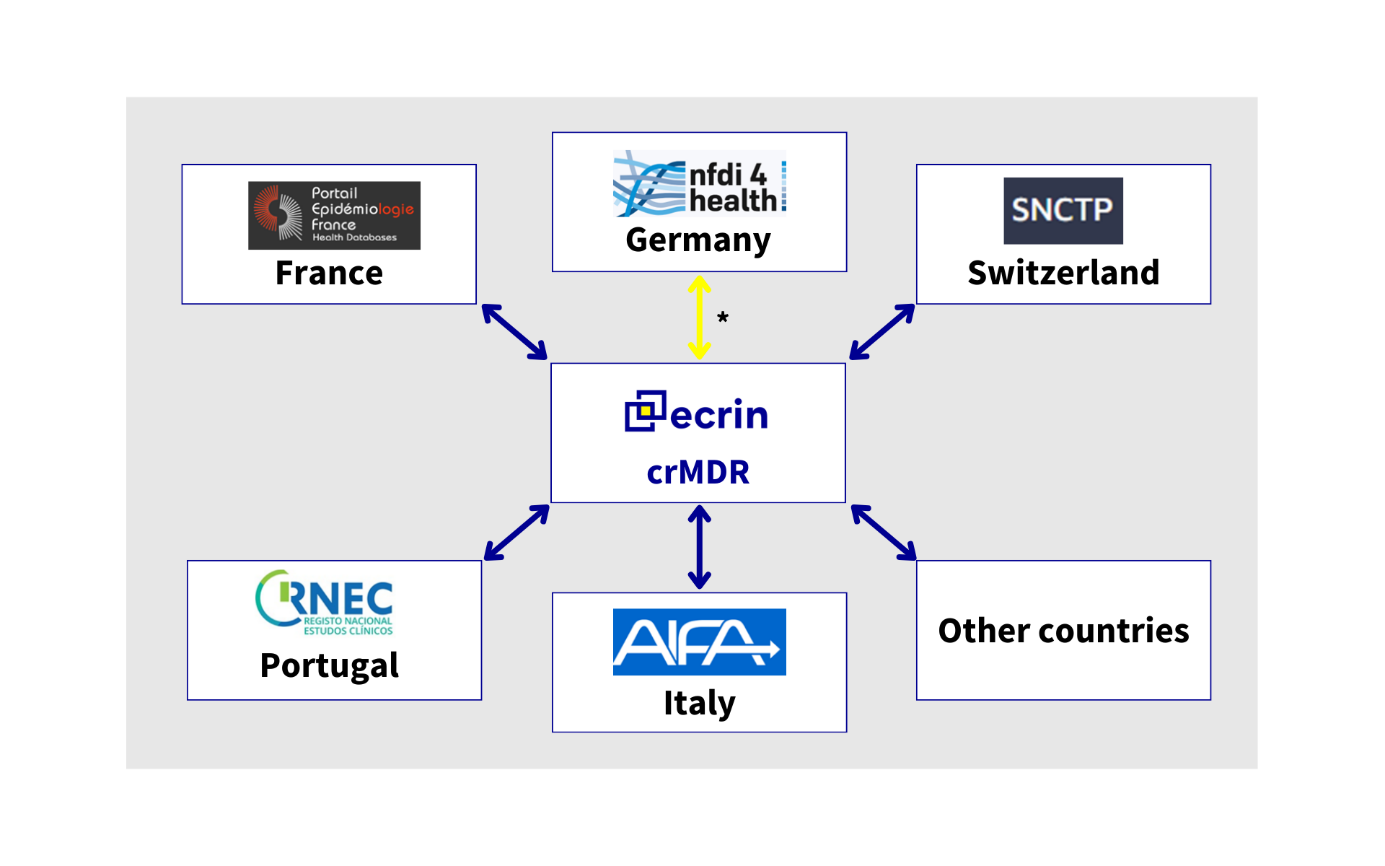
In the final question it was asked whether there is an interest in the National Scientific Network of CTUs to use the repository developed by ECRIN. This repository, named **clinical research Data Sharing Repository**, was developed in the EU-funded project EOSC-Life\* (<https://www.eosc-life.eu/>, received EU funding under Horizon 2020, grant agreement number 824087) with the objective to store and share IPD from clinical trials/clinical studies. France, Germany, Italy and Spain expressed interest. From France it was indicated that such an activity may be useful for academic research and in Italy the wish was expressed to better understand the proposal and to evaluate compliance with national policies. For Germany, a cooperation between NFDI4Health and ECRIN has already been initiated. In 2020, the Spanish Clinical Research Network (SCREN) participated in the clinical research Metadata Repository initiative created by ECRIN with the aim of sharing useful information for the launch of clinical trials related to COVID-19. No interest was declared by 2 countries for various reasons (e.g., practice challenges for Ireland). Two countries (Greece, Portugal) stated that they could not decide now.

**Discussion**

To create the best evidence for treatment of health systems it is necessary to extend the findability of clinical studies from trial registries to registries for observational and health studies. A good example in support of this strategy is the recent COVID-19 (coronavirus disease of 2019) pandemic which dramatically underlined the multi-faceted nature of health research, requiring input from basic biological sciences (e.g. viral characterisation and genomic sequencing), from pharmaceutical technologies (e.g. development and manufacture of mRNA (messenger ribonucleic acid) vaccines), from clinical research (e.g. observational and interventional studies of candidate treatments), from social sciences (e.g. understanding vaccine hesitancy, examining political responses to the pandemic), and from public health and social engineering (e.g. promoting ‘lockdown’ behaviours and mask wearing) (2). Observational studies are part of the complete set of evidence. So, to better support evidence-based medicine, trial registration covering all types of clinical studies/clinical trials is necessary (3).

Clinical trial registries are established tools and are widely used by the clinical research community. Much of the rationale for prospective registration of clinical trials also applies to the registration of observational studies (3). The existing infrastructure for trial registration can be and is used for observational studies but the coverage of the full spectrum of such studies is very limited (e.g. only 20% of WHO ICTRP are observational studies). Therefore, it has been requested for quite a long time to make prospective registration of observational research a reality (4). Meanwhile, several countries have started to build up registries especially for observational studies. In our survey, such activities have been reported by six countries from ECRIN. These repositories are notencompassed in the primary registries of WHO ICTRP. Consequently, a search for this type of study is quite limited.

A logical first step to improve the situation would be to extend the network of registries provided by WHO ICTRP with the registries on observational and health studies reported in our survey. Here the clinical research Metadata Repository crMDR from ECRIN could play a major role. The crMDR covers all primary registers from WHO ICTRP plus ClinicalTrials.gov, Pubmed and some repositories for sharing of IPD (e.g. BioLINCC - Biological Specimen and Repository Information Coordinating Center, YODA - Yale University Open Data Access). The crMDR is based on a standard metadata schema (5). A promising strategy could be to map the ECRIN metadata schema to the metadata schemas of the national registries for observational studies. Initial work has already been done by a crosswalk between the ECRIN’s crMDR metadata schema and the metadata schema of the German Central Health Study Hub of NFDI4Health. Such a process could be extended by linking to other metadata schemas of national registries on observational studies (see figure 3).



**Figure 3: Network of registries for observational studies** \* metadata crosswalk performed

ECRIN would be interest to bring this forward based upon the crMDR and bilateral cooperations with ECRIN member and observer countries. A promising option could be to apply for EU- and/or national funds to kick off this process (e.g., OSCARS Open Calls for Open Science Projects and Services through a cascading grant mechanism; <https://indico.in2p3.fr/event/30390/attachments/80693/118627/OSCARS%20Open%20Calls%20-%20proposals%20guidelines_October%202023.pdf>).

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