Data Valley White Paper

e-Health Data Sharing

Best practices and solutions for data sharing, anonymization, and data lake creation with health data.

ENG Version of the April 2023 DRAFT

Participants in the working table and drafting of the white paper:

Carlo Rossi Chauvenet, Data Valley

Silvia Martinelli, Data Valley - Università degli Studi di Torino

Paola Aurucci, Università degli Studi di Torino

Alessandra Salluce, Università degli Studi di Milano

Piergiorgio Chiara, Università di Bologna

Vanessa Cocca, CRCLEX

Giorgio Presepio, San Raffaele (DPO)

Alexandru Raileanu – AWS

Elena Cappellaro, Astrazeneca

Federica Rizzo, EPEE / Green Innovation Network

Paolo Bartoli, Cloud-R - Soluzioni software per registri di malattie rare

Ruggero Di Maulo, Cloud-R - Soluzioni software per registri di malattie rare

Daniele Panfilo, Aindo - Tecnologia all'avanguardia per la produzione di dati sintetici

Jovan Stevovic, Chino.io - Soluzione software per la gestione del dato sanitario

Ludovica Paseri - Università degli Studi di Torino

Elisabetta Biasin – KU Leuven. Centre for IT & IP Law

Avv. Silvia Stefanelli - Studio Legale Stefanelli&Stefanelli

Abstract

The White Paper of Data Valley "E-health Data Sharing" arises from the need, shared by operators in the sector, to reconstruct the applicable legal framework and define best practices for sharing data and creating data spaces in the healthcare sector.

The first section describes the impact of data analysis in the healthcare sector, the European perspectives for creating dataspaces, and the emergence of the need to identify, define and consolidate models and best practices for anonymization and sharing.

The second section, dedicated to the use of health data for treatment and research purposes, reconstructs the applicable legal framework, differentiating between personal data, anonymous data, and pseudonym data according to the GDPR; analyzing the specificities relating to the processing of health data for treatment and research purposes, also distinguishing between experimental research and observational research; deepening the problems relating to the sharing of "group data".

The third section focuses on the evolutionary profiles to enhance health data among the actors in the ecosystem by creating data lakes in health care to improve research/care through the concentration of data.

Finally, the fourth section describes the technologies for anonymization and synthetic data, the choice of technology, and its implementation.

TABLE OF CONTENTS

Data Sharing in Health Care and the Goals of the White Paper.

Introduction

Carlo Rossi Chauvenet, Silvia Martinelli

The use of data and algorithms for organizing production and bringing supply and demand together has brought about a paradigm shift that has affected both forms of production and exchange, as well as the product itself.

The paradigm shift described is enabled by the creation and management of data flow. These can be personal ones entered by the user or generated in the interaction with the product, or those collected by sensors and related to the surrounding environment, or even those collected by thousands of other applications with which the product and its user necessarily interact.

Thus, data-driven business models are multiplying in recent years and at this moment in history, all based on new forms of using the information collected in them. At the same time, the interest in having access to additional databases necessarily increases, in order to be able to generate new correlations and new services to be proposed to end users, consumer or business or even public entities.

The sharing of data and its reuse in innovative ways for creating new smart products and services, however, face some obstacles.

First, the use of the data, where personal or even where then anonymized to the point of its anonymization, requires as well known and dutiful the application of all the principles, cautions and procedures provided by our legal system for the processing of personal data.

Second, the sharing of data among different entities, private or public, requires agreements, partnerships or the construction of new legal structures for the management of data governance and for the regulation of all potential issues that may arise from the sharing itself. In particular, agreements will need to be made with regard to the possibilities and modalities for future decision-making, the sharing of risks and the predetermination of responsibilities, as well as the protection of the investment made.

Precondition for the sharing itself is, moreover, the encounter that generates it, becoming critical the identification of the partner who is in possession of or who is able to acquire the desired data asset or, on the other hand, manages the interface or product or sensor that dialogues with the user or the environment that one wishes to reach.

Third, but again a fundamental precondition, is technical dialogue and software integration. The latter is, in fact, critical for real-time communication between systems, for data quality, as well as for reaching the end customer itself, accessing the desired interface or product.

"Data Valley" - www.datavalley.it - is a project that was created to address this need for sharing and integration, carefully evaluating contractual and compliance elements as well. It specialized in the analysis of these issues, first by organizing meetings in the form of a symposium between Triveneto businesses and Big Tech, and later by creating a path of systematic analysis of economic, technical and legal aspects for the creation of new partnerships and synergies for data sharing and technological integration.

The initial experience was then continued online with the creation of restricted-participation working tables focused on specific, shared issues and needs, and the first one initiated led to the development of this White Paper.

The working tables were born from a need to connect multiple stakeholders belonging to the same sector but representative of different stakeholder categories, for the identification of sharing needs as well as obstacles in order to work together in overcoming them.

Starting in November 2020, on an almost monthly basis, Working Group members have been meeting to share experiences and needs, identifying and dissecting common needs and issues. Their experiences, discussions, concerns and aspirations led to the development of the White Paper.

The first section of the White Paper is devoted to describing the impact of data analysis in the health sector, European perspectives on the creation of data spaces, and the emerging need to identify, define, and consolidate models and best practices for anonymization and sharing.

The second section, focused on the use of health data for treatment and research purposes, reconstructs the applicable legal framework, differentiating between personal data, anonymous data, and pseudonymous data under the GDPR; analyzing the specificities related to the processing of health data for treatment and research purposes, including distinguishing between experimental and observational research; and delving into issues related to the sharing of "group data."

The third section focuses on the evolving profiles of the leveraging of health data among ecosystem actors for the creation of data lakes in healthcare for the improvement of research/care through data concentration.

The fourth section is, finally, devoted to technologies for anonymization and synthetic data, technology choice and implementation.

Description of the scenario: the impact of data analysis in the healthcare

Paola Aurucci

Over the past 25 years, the invention, development and diffusion of ICT (information and communication technologies) has greatly expanded the scope of data production, collection, storage and sharing[1]. Increasingly large digital databases and increasingly sophisticated systems of analysis have led to the rise of so-called data centrism[2], which has enormous implications for how scientific research is conducted, organized, governed and evaluated[3].

Going into the specifics, what really changes from the past due to the proliferation of devices suitable for digital data recording in heterogeneous environments is that it allows for continuous real-time digital imaging of different social and technical systems, on a global scale and with high resolution of individual behaviors. This new ability to measure humans is accompanied by new ambitions to understand these systems and control them. Not surprisingly, an immediate consequence of the change in the scale of the numerosity of the contactable and measurable population within the medical sciences has been an extraordinary development of observational clinical and epidemiological research on real word data, inclusive of primary and secondary prevention and care in the narrow sense. Such observational studies on large data sets, thanks to the availability of innovative computational technologies, have also made it possible to explore the best combination of available variables in a controlled setting to predict a given outcome (e.g., studies aimed at identifying patients who have a higher probability of benefiting from a specific treatment).

The biomedical sphere, then, has been particularly affected by the digital revolution. The growth rate of electronic data in this context is, in fact, above average. This is occurring by virtue of four major phenomena: (i) digitization of imaging; (ii) digitization of medical records and health files (iii) explosion of the Internet of Things (hereafter "IoT" and (iv) the development of Next Generation Sequencing (hereafter "NGS") sequencing techniques-also called Second Generation Sequencing or High-throughput Sequencing. The latter are employed in the field of so-called "omics" sciences and allow with reduced time and high analytical sensitivity, to acquire a huge amount of data related to different hierarchical levels of biological complexity (DNA, mRNA, proteins, metabolites, etc.). The use of such techniques has made it possible to provide a comprehensive view of the cellular and molecular processes that characterize individuals, contributing to revolutionize the study of complex systems (systems biology), which through integrative modalities and advanced computational models aims to answer complex biological questions such as pathogenesis, natural history and evolution of diseases.

[1] Pagallo, U., Il diritto nell'età dell'informazione, G. Giappichelli Editore, 2014, p. 174.
[2] Floridi, L., The 4th revolution: how the infosphere is reshaping human reality, Oxford, 2014, p. 96.
[3] Leonelli, S., La ricerca scientifica nell'era dei Big Data, Meltemi, 2018, p. 31.

This enormous amount of data, coming from heterogeneous sources that collect and update data for reasons largely unrelated to clinical and epidemiological research, if not properly analyzed and integrated, risks becoming a handicap when one wishes to translate them into new scientific discoveries. Fortunately, the availability of such data also represents a unique opportunity to train machine learning algorithms, a key factor in the development of artificial intelligence, to be used for disease prevention, diagnostics and new drug development. In fact, the analysis of this novel data stream by means of artificial intelligence techniques, and machine learning in particular, makes it possible to automatically identify correlations from which it will be possible to make "predictions" using inductive reasoning and formulating hypotheses. In particular, the use of machine learning to integrate the huge amount of data produced by second-generation sequencing techniques used in molecular biology makes it possible to objectify and quantify the heterogeneous nature of most diseases and the phenotypic variability of individuals at the level of genomics, epigenomics, transcriptomics proteomics and metabolomics, the so-called "panomics." It will then be possible to proceed with increasingly precise patient profiling and sew treatment according to the individual's genetic profile. A further conceptual progression can be identified in precision medicine, defined by the National Institute of Health (hereafter "NIH") as "an emerging approach to the treatment and prevention of disease that takes into account individual variability in genes, environment, and lifestyle,"[4] i.e., that takes into account not only genetic variability, but also environment and microbiota composition. The affirmation of this approach will depend on the integration of huge amounts of data produced by the use of high-processing methods for molecular characterization of patients, together with an equally huge amount of physiological, clinical and environmental data obtained from multichannel technologies such as smartphones and wearable sensors (as well as from information obtained through frequenting compulsive social media) and their analysis by machine learning tools.

We are thus only at the beginning of a process that could result in an epochal revolution in clinical practice and health care, which finds in the data intensive research the crucial element that proposes, raises and creates a number of critical issues and unprecedented questions. In addition to epistemological issues, related for example to the real reliability of the evidence produced by the analysis of heterogeneous data, and technical issues, related to the development of systems capable of safely processing and analyzing a huge amount of data, the most recalcitrant critical issues are ethical and legal. And this applies both to classical retrospective observational research on data from the real world, and to investigations in the field of precision medicine involving the systematic use - often by different research centers - of personal data of a sensitive and ultra-sensitive nature (genetic data) for purposes beyond those for which they were initially collected (secondary use). Indeed, considering the proliferation of digital recording systems, mobile devices, and wearables in the health care environment, as well as the inherent research value of health and genetic data, the rise of data-driven research implies, as pointed out by Mittlestadt and Floridi, "the impossibility of predicting at the time of collection all future uses

[4] National Institute of Health, The promise of precision medicine, reperibile sul sito internet: www.nih.gov/about-nih/what-we-do/nih-turning-discovery-into-health/promise-precision-medicine.

of the data"[5]. This undermines the use of consent as a legal basis for the processing of these data, since to be valid it must be informed and specific, i.e., referring to a specific purpose or purposes, and this is not possible since these data will likely need to be reused, shared, and aggregated to others for research purposes. In such cases, re-contacting each individual patient to inform them about the new research purpose is excessively costly, is organizationally impossible, or could jeopardize the achievement of the research purposes. Such purposes are even unknown at the time of processing in observational research based on the use of machine learning, which is capable of making transformative use of information, that is, identifying correlations invisible to the naked eye of the researcher, not even abstractly predictable prior to data analysis. Such research is, in fact, aimed at identifying the study hypothesis - not test it - and severely challenge the re-consensus approach. Alternative to the latter is anonymization, which, however, is difficult to achieve in a big data context.

European perspectives: the creation of data spaces in the health care sector

Vanessa Cocca

The General Data Protection Regulation (GDPR) has created a level playing field for the use of personal data, including health data. However, the landscape of digital health services, within and between European member states, remains fragmented due to different national regulatory transpositions.

Regulatory fragmentation in Europe regarding the processing of health data is a major obstacle for players in the health sector. As a result, the European Commission considers it essential to strengthen and expand the sharing, use and reuse of data health to boost innovation in the biomedical sector.

The Commission itself will promote, as discussed by Member States on the occasion of the "Recovery and Resilience Facility"[6], the establishment of European common data spaces (data spaces[7]) in strategic economic sectors and areas of public interest, in order to make large amounts of data available to actors in a sector.
Specifically, each common data space will feature a distinctive legislation and governance model based on the relevant sector to ensure full use and interoperability of data[8]. The data space is thus intended to be a tool regulated at the European level and developed in full compliance with

[5] Mittelsadt, B.D. e Floridi, L., The ethics of big data: Current and foreseeable issues in biomedical context, in Science and Engineering Ethics, vol. XXII, n. 2 (2016), p. 303-341.

[6] p. 17, Communication from the Commission to the European Parliament, the Council, the European Economic and Social Committee and the Committee of the Regions - 2030 Digital Compass: the European way for the Digital Decade, Bruxelles, 9 marzo 2021.

[7] A data space is an infrastructure that connects several virtual storage facilities containing only data (not, for example, common areas, system data or programs) and with which it interacts through an API or software.

[8] p. 29 , Comunicazione Della Commissione Al Parlamento Europeo, Al Consiglio, Al Comitato Economico E Sociale Europeo E Al Comitato Delle Regioni - Una strategia europea per i dati, Bruxelles, 19 febbraio 2020.

EU legislation on data protection data and compliant with the highest available cybersecurity standards.

The biomedical-health sphere, by virtue of the peculiarity and implications of the data being processed, represents an area in which data use can have a systemic impact on the entire ecosystem. Accordingly, the Commission proposes the establishment of a European health data space, aimed at: helping health authorities in making data-driven decisions to improve the accessibility, effectiveness, and sustainability of health systems; contributing to the competitiveness of the EU health industry; supporting the work of health system regulators in the evaluation of drugs or biomedical products and the demonstration of their safety and effectiveness; and finally, ensuring citizens' access, control, and portability of personal health data by implementing an electronic health record (EHR) safeguarding privacy.

How the white paper has been developed: the need to identify, define and consolidate models and best practices for anonymization and data sharing in the health care sector

Carlo Rossi Chauvenet

The goal of the white paper is to define the regulatory and technical framework that represents the new level playing field in which healthcare stakeholders are increasingly called upon to operate.

In the traditional relationship between the patient and the physician, important spaces of interaction have opened up, governed by technology, which require substantial investments and a systemic vision. The reference is obviously related to biomedical engineering companies, medical devices and all devices that measure people's lifestyles, telemedicine services to biomedical research platforms.

This domain is expanding greatly, but it is very fragile because it is left to the regulatory choices of individual nation states, which are always particularly constraining in this area. In turn, these choices depend on the assessment of available technologies that is made by individual regulatory bodies who are often influenced by news stories of incidents related to the use of certain technologies in their early stages and the resulting public concerns.

For this reason, it is increasingly appropriate for operators in the entire health sector to define in unified documents the framework of the needs and solutions envisaged in the interest of the patient, self-defining a consensus on regulatory and technological elements to encourage investment and shelter them from regulatory onslaughts in the early stages of development of a highly innovative sector. It is the first step in creating a testbed space for sharing solutions and integrating services along the lines of the "sandbox" model used in the United Kingdom with regard to financial regulation.

On the Data Protection front in health care, the issue is increasingly topical given the need to share and integrate large volumes of personal and non-personal data made possible by the use of innovative data anonymization techniques such as the use of synthetic data.

In the remainder of the paper, the needs of the industry, the current regulatory framework, and the available technological solutions will be analyzed, formulating proposals for advancing the regulatory framework to protect investment in the industry.

The use of health data for treatment and research purposes

Personal data, anonymous data and pseudonymous data under the GDPR

Piergiorgio Chiara

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie ITN EJD grant agreement No 814177

The GDPR applies only to personal data. Non-personal data therefore fall outside its scope. The legal classification of data is therefore a topic of central importance as it determines whether the entity processing the data is subject to the various obligations that the regulation imposes on data controllers. Yet the binary construction of the European data protection regime, five years after the Regulation came into force, still does not provide the legal certainty desired by market actors.

The Regulation defines personal data in Article 4(1) as any information relating to an identified or identifiable natural person. Furthermore, an identifiable person is any natural person who can be identified, directly or indirectly, with particular reference to an identifier such as a name, an identification number, location data, an online identifier, or to one or more features of his or her physical, physiological, genetic, mental, economic, cultural, or social identity.

Before examining in more detail, the test adopted by the Regulations to determine the personhood of data, a second relevant dichotomy should be highlighted in the context of non-personal data. Indeed, some data are always non-personal because they have never concerned an identified or identifiable natural person. Others, on the other hand, are originally personal data within the meaning of Article 4(1) but, as a result of an operation aimed at removing the link with the natural person, become non-personal because the natural person is no longer identified or identifiable. It is especially the latter category of data that gives rise to the aforementioned technical-legal issues that closely affect research, especially in biomedical field.

In this context, Recital 26 of the Regulation sets out the test to be performed to shed light on the different processing techniques that invest the binary distinction between personal and non-personal data. In particular, the case of pseudonymization and anonymization should be analyzed in more detail.

Pseudonymization is conceived by the GDPR as a means of reducing risks to data subjects by "hiding" the identity of individuals in a dataset, for example, by replacing one or more personal identifiers with so-called pseudonyms. Obviously, the technical-logical link between pseudonyms and initial identifiers must be appropriately protected by the data controller.

The risk of re-identification is reduced, and it is certainly true that such processing prevents direct identification of the data subject. Yet, according to Recital 26, personal data subjected to pseudonymization techniques should be considered information about an identifiable natural person and therefore fall under the scope of the Regulation, as it could still be attributed to a natural person through the use of additional information.

Conversely, the same Recital states that the Regulation should not apply to anonymous information, that is, information that does not relate to an identified or identifiable natural person or to personal data rendered sufficiently anonymous that it prevents or that the data subject can no longer be identified.

A closer reading of the text reveals the heart of the Recital 26 test. Indeed, to establish the identifiability of a person it is appropriate to consider all means, such as identification, that the data controller or a third party may reasonably use to identify that natural person directly or indirectly. To ascertain the reasonable likelihood of using the means to identify the natural person, all objective factors should be considered, including the cost and time required for identification, taking into account both the technologies available at the time of processing and technological developments.

The test elaborated in recital 26 of the GDPR essentially embraces a risk-based approach to determine the personhood or otherwise of the data. Where there is a reasonable risk of identification, the data should be treated as personal data. Where, on the other hand, that risk is negligible, the data can be treated as non-personal data, and this is so even if identification cannot be ruled out with absolute certainty[9].

This reading based on the risk approach of the Regulation has found resistance especially in the so-called ‘absolutist’ reading of the Working Party art. 29, followed by some supervisory authorities, such as the French[10] and Irish[11] Data Protection Authorities. This interpretation takes into account all the possibilities and occasions in which anyone would be able to identify the data subject: while the GDPR explicitly refers only to the possibility of identifying the individual, the Working Group goes further, adding to the de-identification test the criteria of (i) linkability of information about the individual in different datasets; and, (ii) inference, i.e., the possibility of inferring, with significant probability, the value of an attribute from the values of a set of other attributes[12].

Thus, the Working Group art. 29 sets a high threshold to be met, establishing its "zero risk test" according to which no risk of re-identification can be tolerated. This would imply a perfect equation between anonymization and deletion: the result of such a technique should be permanent, making it impossible for any technical operation to re-identify the individual to whom the personal data originally referred.

The absolute approach, however, can hardly be sustained: there is a flourishing literature on the non-absolute nature of anonymization[13]. Therefore, if we could never rely on the non-personality of the data, then any information would always remain within the scope application of the GDPR.

[9] Finck, M. e Pallas, F., “They who must not be identified—distinguishing personal from non-personal data under the GDPR” (2020) International Data Privacy Law, 10(1), 11-36.

[10] Commission Nationale de l'Informatique et des Libertés, “Comment prévenir les risques et organiser la sécurité de vos données ?” (2019).

[11] Data Protection Commission, “Guidance on Anonymisation and Pseudonymisation” (2019).

[12] Article 29 Working Party, Opinion 05/2014 on Anonymisation Techniques (WP 216) 0829/14/EN, 3.

[13] Ohm, P., “Broken Promises of Privacy: Responding to the Surprising Failure of Anonymization” (2010) UCLA Law Review, 57(2); Sweeney, L., “Simple Demographics Often Identify People Uniquely” (2000) Health, 671; Narayanan, A., e Shmatikov, V., “Robust De-anonymization of Large Sparse Dataset”(2008) IEEE Symposium on Security and Privacy.

Another reading of Recital 26, so-called relativist, considers only the efforts required to identify an individual, without delving into the murky field of mere theoretical possibilities. Several authors, and to some extent the UK Data Protection Authority[14], have argued that data resulting from anonymization operations by cryptographic techniques should not be considered personal data if two requirements are met: the cryptographic method must be effective, robust, and up-to-date, and the data controller (or any third party) is not in possession of the decryption key, nor is there a reasonable chance that he or she will obtain the key. This reasoning has been particularly successful in the field of cloud computing[15].

However, the most convincing position is the one based on the risk approach, which inspired the Regulation and has been confirmed by the Court of Justice[16]. If there is a reasonable likelihood that certain data, even if subjected to irreversible encryption operations (e.g., salted/peppered hash function) in order to achieve anonymization, can be (re)linked to the natural person to whom they were originally referenced, they must be qualified as personal data. In contrast, if de-identification has been sufficiently robust so that identification is no longer reasonably likely, that data should be considered non-personal[17].

Against this background, on 26th April 2023, the General Court of the European Union (EGC), published its judgment in Case T-557/20, Single Resolution Board (SRB) v European Data Protection Supervisor (EDPS)[18]. The General Court held that pseudonymised data sent to a recipient should not be considered personal data if the party receiving the data does not have the actual means to re-identify the individuals concerned. Interestingly, by building on the *Breyer case*[19], the General Court adopts a *ptima facie* relativist approach towards the re-identification conundrum: EDPS should have ascertained whether the possibility of combining the information that had been transmitted to the recipient of the pseudonymised data with the additional information held by the party transmitting those data (SRB) constituted a means *reasonably likely* to be used by the recipient to (re)identify the individuals to whom the pseudonyms referred to[20]. Thus, the General Court held that the 're-identifcation test' must be carried out from the perspective of the recipient of the data, regardless of the possibility that another party may have to re-identify data subjects (e.g., the sender of the pseudonymised data having access to the database with the original identifiers). It should be noted nonetheless that the EDPS will most likely appeal this ruling before the Court of Justice of the European Union.

[14] Information Commissioner's Office, "Anonymisation: Managing Data Protection Risk Code of Practice" (2012)

[15] Hon, K.W., Millard, C. e Walden, I., "The problem of 'personal data' in cloud computing: what information is regulated? -the cloud of unknowing" (2011) International Data Privacy Law, 1(4).

[16] Case C-582/14 Patrick Breyer [2016] EU:C:2016:779.

[17] Cfr. con AEPD ed EDPS, "Introduction to the Hash Function as a Personal Data Pseudonymisation Technique" (2019)

[18] The dispute relates to Regulation (EU) 2018/1725 on the protection of natural persons with regard to the processing of personal data by the Union institutions, bodies, offices and agencies and on the free movement of such data. However, provided that the definition of the concept of personal data under Art. 3(1) of said Regulation is identical to the GDPR's wording, the judgment can also be used for the interpretation of the application of the GDPR.

[19] Case C-582/14, n. 16.

[20] General Court of the European Union, Case T-557/20, *SRB v EDPS*, ECLI:EU:T:2023:219, para. 104.

Health-related data: treatment purposes and research purposes

Paola Aurucci, Giorgio Presepio

"Health-related data," along with biometric and genetic data, are included by the GDPR in the "Special Categories of Personal Data" (what are referred to in common parlance as "sensitive" or "super-sensitive" data). The identification of these Special Categories of data, made specifically by Article 9 of the GDPR, is functional to the provision of a more restrictive regulation of their processing. A higher protection for this type of data is guaranteed by virtue of their inherent dangerousness, since they not only identify the individual (as it is for common data) but they indefectibly contribute to the construction of his or her identity, and for this reason they are susceptible to be a source of abuse and discrimination if improperly processed. In confirmation that the processing of health-related data (and biometric and genetic data) is even more dangerous than the processing of other special categories of data, paragraph 4 of Article 9 authorizes the Member States to maintain or introduce additional conditions and possibly limitations to the discipline provided by the aforementioned Article 9, which turns out to be only a minimum discipline with respect to this type of data. Article 4 of the GDPR defines health-related data as that "pertaining to the physical or mental health of a natural person, including the provision of health care services, revealing information relating to his or her state of health." Recital 35 specifies a further important aspect, namely the temporal aspect, by specifying that health-related data relate to an individual's physical or mental condition whether past, present, or future. The recital goes on to specify that these are data typically collected (although not stated as an exclusive situation) in the course of registering for access to a benefit and goes on to provide a (nonexhaustive) list of examples of such data: a specific symbol or element attributed to a natural person to uniquely identify him or her for health purposes; information resulting from examinations and checks carried out on a body part or organic substance, including genetic data and biological samples; and any information regarding, for example, a disease, disability, disease risk, medical history, clinical treatments, or physiological or biomedical status of the data subject, regardless of the source, such as, for example, a physician or other health care provider, a hospital, a medical device, or an in vitro diagnostic test. The European Data Protection Board went on to add that information that when cross-referenced with other data is likely to reveal health status or health risks (e.g., the presumption that a particular person is at a higher risk of heart attacks based on repeated blood pressure measurements over a certain period of time), in addition to information collected by a health care provider in a medical record, should also be considered sources of health-related data, self-assessment tests, in which individuals answer questions related to their health (e.g., describing symptomatology) and information that as a result of its use in a specific context reveals the individual's health status (e.g., information related to a recent trip or stay in a COVID-19-affected region processed by a health professional to make a diagnosis). On the basis of these assessments, on the other hand, a mere representation of the subject's physical reality (e.g., his or her picture, audio of his or her voice or heartbeat) should not be considered health-related data if that data is not then processed in such a way as to reveal elements related to the subject's health status. The definition of state of health should then include-in addition to a

pathological condition-both the condition of good health, both physical and psychological[21] -and that of recovery from a disease.
In light of these assumptions and the relevant case law of the Court of Justice of the European Union ("CJEU")[22], it can be inferred that the term "data relating to health" should be interpreted broadly.

The regulations under the GDPR seek to reconcile the protection of the individual, with regard to sensitive information about him or her, with the need for economically and socially relevant activities, such as scientific research, to be carried out. The latter, in particular, enjoys particular favor within the Regulation, which although it does not provide an explicit definition of "data processing carried out for the purpose of scientific research" at Recital 159 states that this assumption "should be interpreted broadly" and "taking into account the Community objective of creating a European research area - as provided for in Article 179 of the TFEU - so that "researchers, scientific knowledge and technologies circulate freely." The same recital goes on to give a wide range of examples of what should be meant by scientific activities in which "privately funded research" as well as "studies carried out in the public interest in the field of public health" are included. There is no doubt that this broad definition is intended to ensure that it includes both clinical trials, funded in most cases by pharmaceutical companies, and observational clinical studies. The " Article 29 " Working Group went on to point out that the interpretation of the term "scientific research" should not go beyond the meaning commonly given to it, i.e., "a research project established in accordance with relevant ethical and methodological standards sectors, in accordance with good practice."

In addition, as it will be seen below, for the first time the GDPR provides a specific exception to the prohibition on the processing of health-related data if it is necessary for such scientific research purposes.

With respect to the "processing of health-related data for scientific research purposes," it is necessary to distinguish between two different uses that can be made of these data. We speak of "primary use" when such data are collected directly for scientific study purposes. Examples of studies in the biomedical field that assume the primary use of health-related data are clinical trials and prospective observational studies. In such studies, the patient's health-related data are in fact collected ab origine for the specific purposes for which the study itself is being conducted and must be fully described to the subject before participating in the research. On the other hand, we speak of "secondary use" when the health data that are used research purposes were initially collected for other purposes (e.g., for treatment purposes within normal clinical practice, previous clinical trials, or previous and different observational studies). This is also referred to as "further processing for research purposes." A typical example of secondary use of health-related data for research purposes is found in retrospective observational studies in which personal data were previously collected for health care purposes or for the execution of previous research

[21] See case C-101/01, Lindqvist, point 50.
[22] Ibidem.

projects or were derived from biological samples taken previously for health care purposes or for the execution of previous research projects.

The distinction between scientific research based on the primary or secondary use of health-related data assumes particular importance in determining the legal basis for processing, information requirements, and the application of the principle of purpose limitation.

The proliferation of digital recording systems, mobile devices, and wearables in health care settings, considering the inherent research value of biometric and genetic health-related data, has triggered an unprecedented proliferation of data-intensive observational studies based on secondary use of health-related data. Health data routinely collected in normal clinical practice are thus continually being reused, shared, and aggregated with others for purposes other than those for which they were collected. Such additional research purposes are even unknown at the time of data access by the researcher in studies involving data analysis by artificial intelligence systems capable of identifying correlations and links invisible to the researcher's naked eye, not even abstractly predictable prior to data analysis, on which to then base predictive models that allow understanding that certain combinations of values of certain parameters are often associated with specific clinical conditions.

Experimental and observational research

Paola Aurucci

Biomedical research in very general terms can be defined as research of a multidisciplinary nature that increasingly employs integrated approaches that make use of complementary notions and methodological inputs typical of different scientific disciplines to understand physiological, pathological, and pharmacological mechanisms. It is preliminarily divided between preclinical research (research that is not conducted on humans) and clinical research (that is conducted on humans). The latter is conducted directly on humans (both healthy and sick) and is aimed at the direct study of disease for the development of new effective treatments for prevention, diagnosis, rehabilitation/assistance, and cure. Clinical research is based on various types of studies using both experimental and observational methodology. For this reason, at the regulatory level, Regulation (EU) No. 536/2014 to define clinical trials first establishes what should be meant by a clinical trial, i.e., " any investigation carried out in relation to human subjects aimed at: a) discovering or verifying the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; b) identifying any adverse reactions of one or more medicinal products; or c) studying the absorption, distribution, metabolism and elimination of one or more medicinal products, in order to ascertain the safety and/or efficacy of those medicinal products. Only in the subsequent Article 2(2) does it specify that a clinical trial represents a subcategory "that meets one of the following conditions: (i) the assignment of the subject to a particular therapeutic strategy is decided in advance and is not part of the normal clinical practice of the member state concerned; (ii) the decision to prescribe the investigational medicinal products and the decision to include the subject in the clinical trial are made at the same time; (iii) additional subjects diagnostic or monitoring procedures in addition to normal clinical practice.

The Regulation then, following an approach that takes due account of international guidelines, particularly that of the United States whose regulations on experimental studies have for several years provided for a classification of these according to level of risk-introduces the concept of low-intervention level trials, in which the investigational drugs have already received marketing authorization, and are used according to the terms of the marketing authorization (comparative studies of authorized drugs) or on the basis of published/documented scientific evidence (e.g., off-label trials). Low-intervention trials are distinguished from "standard" clinical trials in that they involve minimal additional risk to subject safety compared to normal clinical practice. To assess the risk that exists for the subject under study, Recital 11 reminds us that this originates from two areas the investigational drug and the intervention, i.e., the clinical trial procedures. In qualifying which types of clinical trials can be qualified as "low-intervention," committees should therefore focus on whether there is real scientific evidence to support the use of the drug in the trial according to an indication other than that established by the AIC and on the possible risks "additional to normal clinical practice" posed by by the procedures involved in the trial (e.g., diagnostic and monitoring). This type of clinical trial should be subject to less stringent rules regarding monitoring, requirements applicable to the content of the permanent file, and traceability of investigational drugs. Studies classified as observational involve--like experimental studies--establishing a comparison between groups, only the phenomenon under study is not the effect of an experimental intervention, but of an exposure to a risk or protective factor. The latter is spontaneous in nature and is, therefore, not conditioned by the researcher who merely observes what occurs in nature (in clinical practice), not acting on the condition being studied, neither randomly assigning it nor modifying it. Research subjects are placed in comparison groups on the basis of personal characteristics or their experiences not conditioned by the study.

The observational method has developed mainly in epidemiological research, which has been defined as "the study of the distribution and determinants of health-related situations or events in a specific population, and the application of this study to the control of health problems." Observational studies can be prospective and retrospective. In the former at the time the study is planned both the exposure and the outcomes of interest have not yet occurred, consequently the data are collected prospectively and directly for the specific purposes of the study. In the latter, they have already occurred and the relevant data are collected retrospectively-as they are recorded in different datasets-and thus involve further processing of data initially collected for other purposes ("secondary use"). We find the normative definition of an observational study in subparagraph (p) of Article 1 of Legislative Decree No. 200/2007, according to which in such research "medicines are prescribed in accordance with the indications of the marketing authorization where the assignment of the patient to a particular therapeutic strategy is not decided in advance by an experimental protocol, is part of normal clinical practice and the decision to prescribe the medicine is completely independent of the decision to include the patient in the study, and in which no additional diagnostic or monitoring procedures are applied to patients." This definition reveals multiple critical issues. First, it includes only observational drug studies and does not pertain to observational studies in general. There are, in fact, numerous types of studies that methodologically can be classified as observational but do not fall under the definition provided in the regulations because they do not involve prescribing drugs (e.g., epidemiological studies, observational studies of medical devices, studies of biological samples and genetic data; studies of behavior or quality of life) contributing to the patchy regulation of observational studies. Moreover, according to epidemiological theory, the observational study may involve diagnostic and evaluative procedures that are not routine in the clinical practice of the participating subject, and therefore do not qualify as merely "additional" to them.

A partial remedy was AIFA's Guidelines for the Classification and Conduct of Observational Drug Studies. In that document, the following are included in the definition of "current clinical practice": "questionnaires, interviews, diaries, health economics and drug economy surveys, subjective assessments by the subject of his or her own health status, rating scales and blood chemistry tests, the use of which is justified by the study protocol." Ultimately, the national framework proves to be wholly deficient in regulating and classifying the various types of observational studies that can be conducted in health care and epidemiology. In Law No. 3/2018, "Delegation to the Government on the subject of clinical trials of medicines as well as provisions for the reorganization of the health professions and for the health management of the Ministry of Health," the need for a new regulatory instrument - of a binding type - is highlighted. relating to observational studies in the biomedical and health fields.

Broad Consent and Data Altruism Consent

Recital 33 of the GDPR states that «it is often not possible to fully identify the purpose of personal data processing for scientific research purposes at the time of data collection. Therefore, data subjects should be allowed to give their consent to certain areas of scientific research when in keeping with recognized ethical standards for scientific research. Data subjects should have the opportunity to give their consent only to certain areas of research or parts of research projects to the extent allowed by the intended purpose». However, it is still not clear whether the use of *broad consent*, although perhaps it would be better to say *multi-layered consent,* as a legal basis for further processing personal data, by the same controller or a third party, is possible for research purposes. In the *Document on response to the request from the European Commission for clarifications on the consistent application of the GDPR, focusing on health research* the EDPB precises that the phrase «broad consent» cannot be found either in the Recital and/or the GDPR and in its *Guidelines 05/2020 on consent* stressed that Recital 33 «does not the obligations with regard to the requirement of specific consent» and personal data may be processed in the context of research, on the basis of consent, «only if they have a well described purpose». EDPB underlines that within a specific scientific research project this recital «allows as an exception that the purpose may be described at a more general level» when is not possible to fully specify it at the time of data collection. Furthermore, it stresses that that when special categories of data – such as health data and genetic data – are being «applying the flexible approach of Recital 33 will be subject to a stricter interpretation and requires a high degree of scrutiny » without further specification. In these residual cases, the EDPB suggests as a tool to «to ensure the essence of the consent requirements», such as granularity and specificity, a sort of «progressive consent». This model of consent implies that as the study progresses and secondary research purposes (wrongly identified by EDPB as «specific stages of a research project») - already known at the moment of the collection, even if at general level - become more specific, the controller will have to contact the subject again to obtain specific consent obviously «before that next stage begins». This consent «should still be in line with the applicable ethical standards for scientific research», which implies, at least at the Italian level, the existence of a research project drawn up in accordance with the methodological standards of the relevant disciplinary sector (art. 3 of the Rules of Conduct for the processing for statistical or scientific research purposes, published on 14 January 2019) and that it has obtained the approval of the competent Ethics Committee. At the same time, the controller must apply appropriate safeguards, as stressed by Article 89 such as anonymization (which remains the preferred option where it was possible to obtain the same results of a research conducted with personal data), minimization, data security and measures aimed at ensuring the principles of transparency. This model of «progressive consent» suggested by EDPB is not particularly original-ethical and could perhaps be used in prospective (short-term) observational studies but it is certainly not very functional for biobanks, which collect thousands of biological samples, for various pathologies to use/share in the context of various research projects, many of which are not available at the time of collection, but that follow each other over the years. The constant recontacts and reconsents of the data subjects are problematic even when the study lasts for several years. It is the case, for example, of Master Observational Studies (called "MOT")[23] and prospective-retrospective observational studies that aims at creating registers and databases for studying the population affected by a specific pathology, through present and future studies. In these cases, the data subjects could turn out to be deceased over time, become untraceable or no longer able to give specific consent, without considering all the problems, both ethical and administrative, associated with recontacting. However, it is necessary to mention that precisely regarding one study which envisages the creation of a database «on which to build future analysis and studies aimed at improving knowledge and clinical practice in the sector of pathologies of the thoracic district»(called "DB Torax"), the Italian Data Protection Authority embraced this proposed solution. Consequently, it is not enough that data controller, the University Hospital of Verona, would identifies nine "macro" areas of investigation of the future studies in the data protection information notice given to the data subject for the collection and storage of their data in the database, and for which the University asks a second consent, but the controller should also collect a specific consent for each further and specific study - that is going to be based on a specific research protocol – when conducted with the data stored in the database DB Torax. As stressed by the Italian Coordination Center of Ethics Committee this concept of clinical and healthcare research conducted through closed protocols, clearly segmented in different stages, where data processing activities are pre-analytically determined and privacy roles are clearly allocated, primary and

[23] The Master Observational Trial (MOT) is a new model of master protocol that hybridizes the power molecularly based master interventional protocols with the richness of real-world data. It can be described as a series of prospective observational studies that are tied together through a common protocol, infrastructure, and organization. Dickinson *et al.,* *The master observational trial – a novel method to unify precision oncology data collection,* in *Journal of Clinical Oncology*, XV, 2020 *suppl,* e19313.

secondary purposes of the study are fully specified at the outset, does not reflect the contemporary methodological approach, increasingly oriented towards expanding the boundaries of protocols which become interconnected and open. This method of conducting the health and clinical investigations cannot be reconciled with the principle of granularity of consent, meaning that each individual purpose should be identified in subsequent protocols an consented by de data subjects, which risk at, on the one hand, preventing the patient from participating in the study, and on the other, hindering the process of producing medical-scientific knowledge.

This said, should be mentioned that the Data Governance Act (from now on “DGA”, which aims to facilitate the re-use of personal and non-personal data held by public sector bodies, while fully respecting fundamental rights, introduces the concept of data altruism which is defined as «voluntary sharing of data based on consent by data subjects to process personal data pertaining to them [...] without seeking or receiving a reward [...] for purposes of general interest, defined in accordance with national law where applicable, such as [...] or scientific research purposes in the general interest» The DGA provides - in art. 25, par. 1 - that in order «facilitate the collection of data based on data altruism, the Commission shall adopt implementing acts establishing and developing a European data altruism consent form, after consulting the European Data Protection Board». The use of personal data for the altruistic purposes must be based on a legal basis/condition of lawfulness provided for by the GDPR. Recital 50 of the DGA suggests that, in general, «typically, data altruism would rely on consent of data subjects within the meaning of Article 6(1), point (a), and Article 9(2) ». However, the consent, which is given for unspecified future research purposes, although of general interest, cannot satisfy the specificity requirement set forth in art. 4, par. 11 of the GDPR. A possible recourse to a multi-layered consent, even if the DGA expressly refers to recital 33, is not a viable option given the restrictive interpretation of the EDPB. A valid alternative to the use of consent as a basis of lawfulness is given by art. 6, par. 1, lit. and of the Regulation, exploitable in the hypothesis in which data processing is necessary for the performance of a task carried out in the public interest (art. 6, par. 1, lit. *e*), in conjunction with the art. 9, par. 2, lit. *j* when the data processed include particular categories of data, which also include health and genetic data. In this case, consent could be considered as a measure aimed at guaranteeing legal certainty and greater transparency, as envisaged by the DGA itself in recital 52. However, this solution does not seems entirely exhaustive since both of the aforementioned legal bases/condition of lawfulness (art. 9, par. 2, lit. *j*) must be based on Union or Member State law which shall be «proportionate to the aim pursued, respect the essence of the right to data protection and provide for suitable and specific measures to safeguard the fundamental rights and the interests of the data subject». However, such laws it is rare that have been already adopted. Furthermore, this solution it is also in partial contradiction with the DGA itself as it would prevent the interested party from subtracting his data from a specific processing operation through the withdrawal of consent, as foreseen in art. 25, as in this circumstance the data controller could lawfully continue the processing that is based on another legal basis. This would undermine the ultimate objectives of the European data altruism consent form: to ensure greater legal certainty in the context of the use of scientific research data, to guarantee greater transparency for data subjects regarding who accesses their data and for which purposes. Both purposes are prodromal to promote the trust of individuals in health data sharing.

Granular data, clusters, and groups

Alessandra Salluce

The increasingly pervasive use of IT tools and resources has led, as also mentioned in the previous Paragraphs, to the production and circulation of a truly impressive amount of data. However, one should not be surprised: the post-modern era, characterized by so-called "data-driven" business models, represents nothing but the natural evolution of the operational paradigms adopted in all productive sectors, and is undoubtedly doomed, in the near future, to further expansion.

The healthcare and research sectors are also involved: as an example, one only needs to think of the ever-increasing number of apps on the market capable of collecting in real time numerous personal information of a particular nature, as well as the use - increasingly frequent - of technological tools in the performance of more traditional medical activities or, again, the role of research, which, since its beginnings, has been nourished by datasets, but now has at its disposal increasingly cutting-edge tools that enable it to process once unimaginable masses of data.

That being said, on the one hand, there is no denying the absolute usefulness of such a development on the technological front - which, in the health field, has enabled the achievement of once unimaginable milestones - on the other hand, it is important to recognize the existence and relevance of the right to privacy, which is incumbent on each individual, especially in relation to certain types of information.

It is necessary, therefore, to find a "balance point," which allows for the need for knowledge required for certain purposes to be met, especially where related to collective interests worthy of satisfaction, such as health and progress in the medical field, but, at the same time, to protect the privacy of the individuals involved, while also taking into account the critical issues arising from the use of algorithms and the possibility of inferring personal information through data correlation. This crucial node, moreover, is linked to several aspects, including ethical ones, which primarily concern the possibility of giving rise to discrimination. In addition, along with the more strictly legal aspects, it is necessary to include in the analysis also the more technical aspects, especially related to the security of the information and the methods chosen for storage, access and transmission. In the context of health research, moreover, access to data does not concern so much a problem from the authorization point of view, since the transmission of the same is certainly authorized and necessary, but rather from the technical-organizational point of view, since the most critical aspect is related to the choice of the modalities of release of the information: from this choice, in fact, violations could result to the most confidential sphere of the individuals belonging to the sample to be analyzed, where from the data released, whether in granular or aggregate form, more intimate aspects could be deduced or, in the most serious, completely reconstruct the identity of the subject.

Within this complex framework, the application of data release techniques, combined with others of a more strictly IT nature aimed at preserving the security of information, can make a significant contribution[24].

On this point, as a preliminary matter, it is necessary to clarify the differences - mentioned just above - with regard to the type of data released for research purposes: in this regard, one speaks of "microdata" when the information contained in the statistical database is "pure," single; one speaks instead of "microdata" when the information is released in aggregate, statistical form.

In turn, the data, whether released in the form of microdata or macrodata, can be aggregated, going to compose groups, or clusters, on the basis of certain parameters that they have in common, depending on the purpose of the analysis to be conducted. In this case, however, the choice of grouping criterion must be well thought out, since a suboptimal choice may make the path to achieving one's research purpose more difficult, as well as, in some cases, lead to untrue results. Choosing the type of data best suited to our purpose, in any case, presents several critical issues from the point of view of privacy and personal data protection, since not only from such a choice derives the very application of the GDPR-which applies, as is well known, only to personal data, thus excluding anonymous data, assuming they really are-but also the application of the de-identification or pseudonymization measures deemed most appropriate. Relative to this aspect, it is possible to discern some substantial differences in the release of data in "pure" or aggregated format. First of all, pure data is the one that, by definition, is more delicate and deserving of stronger protections: if adequate data protection techniques are not applied, in fact, it is possible to trace back much more easily to the subject to whom they refer and, consequently, also to deduce additional information pertaining to his or her person. This can generally occur in two specific cases:

- when there is a particularly "conspicuous" piece of data within the dataset (such as may be, in a socioeconomic analysis, a salary much larger than others in a database confined to a small geographic area);
- when the data within the database are easily correlated with external information (this occurs when there are numerous matching attributes in the two related databases and the information in them is very accurate and detailed).

Obviously, individuals with peculiar or, even, unique characteristics are more exposed to the so-called "disclosure risk," which involves the identification of the individual or the inference of certain data, in some cases of a particularly confidential nature. Moreover, the two possibilities just outlined become more substantial where particularly accurate data are published and there is more than one external database with which to make connections.

Even the release of data in aggregate form, in any case, is not without risks and critical issues of this sort. First of all, it is worth specifying the existence of two possible forms of macrodata release: so-called "frequency tables" report the exact number or percentage of subjects sharing that particular attribute; "magnitude tables," on the other hand, report aggregate values (generically in the form of a mathematical mean) related to a particular attribute under analysis.

[24] *On this point, it should be specified that while cybersecurity is concerned with the security of information systems and the information flows exchanged through them, providing tools aimed at countering possible infiltration or, more generally, damage to software, hardware, or compromise of data security, data protection techniques are aimed at preventing the correlation and inference of information and identification of individuals.*

Of the two, the latter represent the more problematic ones, since the protection techniques applicable to frequency tables-such as, for example, sampling - may prove insufficient.

It was seen just above how the data released in its "pure" form presents more critical issues from the point of view of data protection, where even the application of specific techniques devoted to this (such as, among others, sampling, generalization, suppression or the addition of "noise") may in many cases allow for the re-identification of the data subject or the inference of other peculiar personal characteristics of the data subject. To assess more realistically the protection of the anonymity of the subjects represented in the dataset, however, it can be very useful to apply the parameters of k-anonymity, l-diversity and t-closeness[25] which allow, through different methods, to add in different and gradually increasing degrees of difficulties in the actual identification of the individual depicted in a given analysis group. These have been joined in recent years by more innovative techniques involving the addition of so-called "noise," such as differential privacy.

What has just been observed with reference to microdata is also valid, albeit with some exclusions, in the case where one has opted for the release of macrodata: the risks one may run into are the same, although the possible data protection techniques applicable are different. These include, but are not limited to, value sampling or the application of "threshold rules" or other special rules.

The main, and underlying, problem with both types of datasets discussed above can ultimately be channeled into the problem of anonymity: when can it be said with reasonable certainty that a piece of data has been rendered anonymous? And when, after applying one of the techniques known to date to protect the privacy of the individual, can one have less fear of possible re-identification?

In addition to such questions of a more purely technical-legal nature, those of an ethical derivation are also emerging more and more powerfully: for example, what are the most correct criteria for the homologation of individuals and their grouping into clusters? What are the possible consequences of a "privacy leak"? What are the discriminations that might result in the reuse of such data-even in aggregate form-for further purposes, especially where processing is done in an automated form?

These are crucial questions, to which too little attention is still paid in many cases, but which, especially in the health field, can lead to truly worrisome implications.

Health data and Open Science

Ludovica Paseri

In the current context of profound transformation of the health sector, in which data are becoming increasingly important, and in the light of the purposes of this white paper, i.e., shaping the legal framework and identifying the most suitable best practices, it is necessary to

[25] *The property of "k-anonymity" allows for the identification, within a group, of at least k individuals who have a characteristic in common; the property of "l-diversity" indicates the amount of different sensitive attributes that each individual represented in a dataset must have to ensure a certain value of anonymity; the property of "t-closeness," on the other hand, aims to redistribute the data so that among the entire distribution of records and a selected part of it are very similar.*

draw attention to Open Science policies and to understand whether and to what extent they concern health data.

Open Science represents a new approach, oriented towards the openness of every phase of the scientific research process: starting with an increased access to data; moving on to the openness of the methodologies adopted; also involving the dissemination phases of the results, favouring open access to scientific publications and the adoption of open practices in education and the dissemination of knowledge. If Open Science only twenty years ago was a set of instances brought forward by a part of the scientific community, today it constitutes a real strand of European policies. Indeed, Open Science is the approach to scientific research recognised by the European institutions, characterised by the principles of openness, cooperation, inclusiveness and transparency, and capable of taking full advantage of the use of new technologies, from Machine Learning (ML) to robotics, from Artificial Intelligence (AI) to High Performance Computing (HPC). This openness is certainly not reflected in an indiscriminate open access to data, methodologies, protocols and research results: the formula underlying open science is "as open as possible, as closed as necessary". This formula emphasises that at the basis of openness and sharing it is necessary and crucial to balance openness against possible opposing interests, such as copyright, personal data protection, public safety, etc. Recognition by European instructions has mainly taken place in two legal texts: the Horizon Europe Regulation, which dedicates Article 16 to the subject, entitled "Open Science"[26]; and the Open Data Directive, Article 10 of which is addressed to "Research Data"[27].

Apparently, health data would not seem to be involved in European and national Open Science policies. Health data are personal data, as such subject to data protection legislation: this aspect plays a major role in the balance between sharing and closure. However, a closer look reveals that the Open Science approach largely entails health data, essentially for three reasons. First, although health data are personal data currently the debate about their sharing and the benefits emerging from such sharing is ongoing and initiatives such as the European Health Data Space confirm this. Moreover, while at first glance the approach to Open Science would seem to be aimed mainly at the area of scientific research financed in part or in its entirety by public funds, on a more careful analysis the situation turns out to be different. The scientific research scenario is currently undergoing a profound change: today, many research sectors are characterised by a profound intermingling of the public and private sectors, so that it is sometimes very difficult to draw clear boundaries. Open Science policies necessarily also take this dimension of transformation into account, giving attention to hybrid contexts, which also involve private actors, such as the health sector. An emblematic example is represented by

[26] Regulation (EU) 2021/695 of the European Parliament and of the Council of 28 April 2021 establishing Horizon Europe – the Framework Programme for Research and Innovation, laying down its rules for participation and dissemination, and repealing Regulations (EU) No 1290/2013 and (EU) No 1291/2013 (Text with EEA relevance), ELI: http://data.europa.eu/eli/reg/2021/695/oj.

[27] Directive (EU) 2019/1024 of the European Parliament and of the Council of 20 June 2019 on open data and the re-use of public sector information, ELI: http://data.europa.eu/eli/dir/2019/1024/oj.

the European Open Science Cloud (EOSC) project: a European, federated space allowing "1.7 million European researchers and 70 million science and technology professionals a virtual environment with free, open and seamless services for the storage, management, analysis and re-use of research data, across countries and scientific disciplines"[28], also involving the private sector.

Lastly, Open Science policies pursue, first and foremost, a broad goal that necessarily also interests the health sector: the Open Science approach intends to promote a thorough rethinking of the scientific research process, in the light of the profound transformation triggered by the digital revolution, so as to take full advantage of the use of new technologies. This rethinking is intended to generate a convergence of interests between sectors pursuing different agendas, such as the private and public sectors. The Open Science approach aims, in fact, to promote an awareness of the assets of the data processed for research purposes, first and foremost promoting good management of these data in order to ensure high quality. In the health sector, having high quality data is crucial, precisely because of what is at stake and the relevance of underlying values and interests.

How, then, can we promote good management of research and health data? A fundamental aspect of the Open Science approach, with specific regard to research data, is the adoption of the so-called FAIR data principles. FAIR is an acronym that indicates four characteristics that data must possess in order to be defined as well constructed and managed from a technical point of view: findability, retrievability; accessibility, interoperability; and, finally, reusability, reusability. Each of these characteristics is further specified by a series of elements, summarised below.

- The "findability" represented by the presence of rich metadata, capable of providing a description of the data itself that is useful to human and artificial agents, and of unique identifiers, guaranteeing the retrievability of such data over time.
- The "accessibility", then, should not be confused with openness tout court. Rather, it represents the concrete traceability of the data, i.e., its potential openness. In order to be defined as accessible, research data must be located in institutional or sector repositories, which are validated and commonly accepted by the scientific community of reference.
- The "interoperability" describes the need to provide data with a formal language, vocabularies and ontologies that effectively enable the re-use of such data.
- The "reusability" refers to the set of features, also of a legal kind, that make it immediately apparent to third parties what can be done with that data set. Consider, first, the choice of the most suitable licence for use on the data, which makes it immediately evident what operations can be carried out, from a legal point of view, without infringing the rights of any actor involved.

[28] Communication of the European Commission, *European Cloud Initiative - Building a competitive data and knowledge economy in Europe*, COM/2016/0178 final, ELI: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=COM%3A2016%3A178%3AFIN.

The FAIR data principles formally outlined in 2016[29], which are the result of a collaboration between several research actors, both public and private, do not represent the only possible way to ensure good data management: the FAIR principles, in fact, are not standards, but rather guidelines, useful to harmonise the management of research data, to allow them to be profitably shared. Good technical management, in fact, becomes an essential precondition for proceeding with the sharing and re-use of research data in general, and health data in particular.

In the legislative framework, the FAIR data principles are specifically mentioned in the aforementioned Open Data Directive, in Article 10, entitled "Research Data". Despite the fact that this legal provision deals with publicly funded research data, the adoption of the FAIR data principles can also be considered as *best practice* in the management of health data, beyond their ownership.

If the intention is to foster data-driven scientific research and healthcare, it is first of all necessary to harmonise the management practices of such data, to make their processing as transparent as possible and to be able to fully exploit their potential. The intertwining of the public and private sectors is emblematic in the health sector, and harmonising data management from a technical point of view is an excellent starting point for establishing fruitful interaction.

Real World Data: New Horizons for Data Processing

Avv. Silvia Stefanelli

On 26 July 2022, the Centro Coordinamento Nazionale Comitati Etici (CCNCE), established at the AIFA Agenzia Italiana del Farmaco, published a note entitled OBSERVATIONAL RESEARCH: A PILAST IN THE KNOWLEDGE PRODUCTION PROCESS.

It is a document that appeared on the website at the end of July 2022 and which (in my opinion) has an impressive scope.

It, therefore, deserves a thorough analysis.

The CCNCE Note originates in the Decree of 21 November 2021 Measures to facilitate and support the conduct of non-profit clinical trials of medicinal products and observational studies and to regulate the transfer of data and results of non-profit trials for registration purposes, pursuant to Article 1, paragraph 1, letter c) of Legislative Decree No. 52 of 14 May 2019: what everyone calls, more succinctly, the Data Transfer Decree.

This Decree, in addition to establishing how data, collected in the context of a non-profit clinical trial, can be transferred, also opens the door to a redefinition and "rethinking" of the entire (complex and sometimes confusing) world of so-called "observational studies" in the light, of course, of the new EU framework defined by EU Reg. 2015/536.

[29] M. D. Wilkinson, *et al.*, "The FAIR Guiding Principles for scientific data management and stewardship", *Scientific data* 3.1, 2016, pp. 1-9; and on the application of FAIR principles to research software, see: A-L. Lamprecht, *et al.*, "Towards FAIR principles for research software", *Data Science,* 3.1, 2020, pp. 37-59.

More precisely, the Decree (implementing Article 6 paragraph 6-ter of Legislative Decree 200/2007 as amended by Legislative Decree 52/2019) establishes

- that "*observational study*" means "*studies referred to in Article 2(2)(4) of Regulation (EU) No 536/2014, the protocol of which has as its object the study of drugs in normal clinical practice according to the authorised indications. Observational studies may be either non-profit or for-profit [...] in art. 1 paragraph 4 letter c)*";
- and that "*new guidelines for the classification and conduct of observational studies on drugs shall be defined by order of AIFA*".

Within this last point, the note of the CCNCE introduces evaluations and indications in relation to a particular and more specific 'category' of observational studies: those in which the health care professional (researcher) merely records what is happening in concrete reality.

Thus it reads:

> *This document is concerned with observational studies understood in their meaning of studies characterised by the absence of active intervention on the part of the researchers, thus defined here as studies in which the researcher does not determine the assignment of subjects to the various study groups, but merely records (observes) what happens in reality*

In essence, here we do not have a clinical protocol with an end point, but only the observation, collection and recording of data emerging from everyday reality.

We do not use the term Real Worl Data, but that is what we are talking about.

In fact, on the Digital Health Europe website, RWD is defined as follows

> *real world data is big data, referring specifically to any types of data not collected in a randomised clinical trial. This data can complement randomised clinical trial data to fill the knowledge gap between clinical trials and clinical practice, provide new insights into disease patterns and help improve the safety and effectiveness of health interventions (EU definition).*

Having clarified the scope of application, let us see what the Note states, particularly in relation to data processing.

First of all, the National Coordination Centre recommends that the Ethics Committees adopt an attitude of maximum simplification of the fulfilments connected with the issue of data protection "*...by removing or limiting as far as possible the formal obstacles that an interpretation of the legislation, based on a predominantly 'interventionist' and 'single-use' approach, still poses to the use and re-use of research data*".

In essence, simplify and start thinking that the 're-use of data' is not taboo.

And here we have the first big opening, also from a purely cultural point of view.

It is well known, in fact, that Article 6(4) GDPR expressly admits the possibility of re-using data for a purpose other than that for which the data were collected, provided that the use is assessed as 'compatible', and also Article 5(b) establishes, in particular, a sort of presumption of non-incompatibility for secondary use in the context of scientific research.

It is also well known that, in Italy, this legislative openness of the GDPR is severely limited by Article 110-bis of the Privacy Code, which binds the re-use of data to an authorisation by the Garante, which may be specific or of a general nature (Article 110-bis paragraph 3).

Now, apart from the fact that an authorisation regime really seems to negate the underlying philosophy and logic of the GDPR (which works all on the principle of accountability), there is a bit of interpretative confusion here because it is not clear (and is being debated among insiders) whether the Provvedimento Garante Privacy bearing the prescriptions relating to the processing of special categories of data, pursuant to art. 21, paragraph 1 of Legislative Decree 10 August 2018, no. 101 for the part concerning Scientific Research can be considered a general provision legitimising the re-use of data pursuant to Article 110-bis: this in view of the fact that it represents the evolution of the previous Authorisation 9/2016, which certainly has a general scope, which implements Article 21 Legislative Decree 101/2018 and which is published in the Official Gazette (my personal opinion is that it can be considered a general authorisation, but I am not aware that there are any positions of the Garante in this sense and therefore the public structures are all very reluctant).

From this point of view, the Note, while certainly not being able to overcome the legislative dictate tout court, does, however, strongly call on the legislator to review the matter in its entirety in a much less restrictive sense, also highlighting the importance for the country of reusing data and pushing for an interpretation that favours such reuse.

The second major opening of the document concerns the legal basis: it is stated that the re-use of data can also find its legal basis in legitimate interest (Art. 6(1)(f) GDPR).

The legal argumentation supporting this opening is very interesting

> "*as a 'source' of knowledge significant for the scientific community, such data must be able to circulate as freely as possible within it. Especially when the purposes of the research are observational (in the sense considered here), it should therefore be possible to have recourse to alternative legal bases to facilitate the (re)processing of the data de quibus, without having to depend every time on a new consent of the person concerned - with the only limitation of a prior appropriate pseudonymisation/encryption of the patient's identity - thus reasonably and effectively balancing the "right of the individual and the interest of the community*" (Art. 32 of the Constitution).
>
> And again
>
> *from this point of view a reference to legitimate interest as a possible legal basis for treatment could, within the limits seen above, benefit the promotion of observational research.*

Here you are 'cleared through customs'. for the first time, I would say, by an institutional body of this level, that sort of 'implicit obligation' to always and in any case use consent, opening the way to other legal bases (moreover, there would be much to discuss as to whether consent, for this type of processing, can be considered truly 'free').

Regarding legitimate interest, it has to be pointed out that this legal basis (obviously combined with one of the exceptions of Article 9) may in some ways simplify the procedure with respect to consent, but it still requires other (and higher) levels of attention.

It can be rightly used solely after the so-called balancing of interests has been carried out.

On this point, the judgment of the Court of Justice (Second Chamber) of 4 May 2017 - C-13/16 established a three-step test:

1. the establishment of the existence of an interest on the part of the data controller,
2. the processing of the data must be necessary for that interest;

3. the interest of the data controller must outweigh that of the data subject (balancing of interests), - and thus the processing cannot be justified (as lawful) if it entails detrimental effects on the rights and freedoms, or legitimate interests, of the natural person.

Each stage consists of an assessment separate from the others.

A final consideration as to why this note is so important. Firstly, because it was issued by the national coordinating body of the Ethics Committees: it stands clear that the Committees can decide independently, but it is equally clear that this is a pivotal input. Secondly, because the issue of Real World Data is one of the crucial junctions in the health sector today.

Indeed, there is no doubt that the current digitisation of the health service and the one to come with the NRP will lead to a significant production of digital data in healthcare.

Such data originate from patient, but can also play a key role not only in the clinical field and/or to improve drugs and devices, but also for the system governance.

The scope becomes clear if one looks at the path that Europe has taken with the European Data Strategy and, in particular, in the architecture of the Proposal of REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the European Health Data Space.

In this context, the value of real-world data is highlighted further in the recent EU Document Study on the use of real-world data (RWD) for research, clinical care, regulatory decision-making, health technology assessment, and policymaking (2021). And it is precisely because of this value and scope that we cannot lag behind.

Evolving profiles of health data valorization among actors of the ecosystem

Data access and security in sharing: the European perspective

Vanessa Cocca

Moving our analysis to the European level, it is worth noting that there have been numerous European impulses over the past few years to digitize the health sector and to sharing of health data[30]. Key action points include interoperability of information systems, data security and privacy-enhancing technologies, improved digital service infrastructure for eHealth, cross-border exchange of health data, common disease registries and platforms, tools for rare disease research, prevention and control of cross-border health threats, better use of European funding, and sharing of best practices.

Health and care systems need deep reforms and innovative solutions to become accessible and effective in providing care to European citizens. Data sharing is an essential step in achieving these goals: however, data are often available in formats that do not guarantee their interoperability and are often managed in ways that are disparate both across member states and within national health systems[31].

The emergency context related to the deployment of Covid-19 showed the potential and paved the way for the widespread use of innovative medical solutions, the use of telemedicine and remote assistance. Digital technologies can enable citizens to monitor their health status, prevent the onset of new diseases, and streamline the operation of healthcare systems. However, the health crisis has also exposed the vulnerabilities of the digital space, its dependence on critical infrastructures, often not based in European territories; highlighted dependence on a few large tech companies; seen an increase in the influx of counterfeit products and cyber theft; and amplified the impact of misinformation on our democratic societies[32]. In this regard, the European Commission estimates that the introduction of greater integration of online services, improved infrastructure for electronic transmission, and access to data could lead to benefits of up to €120 billion per year[33].

Building a common, multi-purpose pan-European interconnected infrastructure for data processing to be used in full compliance with fundamental rights, developing real-time peripheral

[30] See Strategy for a Digital Single Market in Europe, COM(2015) 192 final, 2015.

[31] COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS on the. digital transformation of health and care in the digital single market, empowering citizens and creating a healthier society," COM(2018) 233 final.

[32] COMMUNICATION FROM THE COMMISSION TO THE EUROPEAN PARLIAMENT, THE COUNCIL, THE EUROPEAN ECONOMIC AND SOCIAL COMMITTEE AND THE COMMITTEE OF THE REGIONS "2030 Digital Compass: European way for Digital Decade," COM(2021) 118 final. Compass: European way for Digital Decade," COM(2021) 118 final.

[33] Ibidem 8.

capabilities to serve the needs of end users close to where the data is generated, designing secure, low-power and interoperable middleware platforms for sectoral uses, and enabling easy exchange and sharing of data are among the priorities the European Union has identified in the Digital Compass 2030[34].

This vision has been described and incorporated within the EU4Health[35] Program for 2021-2027, which aims to digitally transform health services, promote interoperability, and develop a European health data space. EU4Health represents the European Union's response to the deployment of Covid-19. With an investment of €9.4 billion, EU4Health becomes the largest ever health program in terms of financial resources, and will provide funding to member states, health organizations and NGOs.

The program will also fund actions related to the creation of the European Health Data Space, among others. The creation of a European Data Space is one of the Commission's priorities for 2019-2025, including in the health sector. A common European Health Data Space will promote better exchange and access to different types of health data (electronic health records, genomic data, data from patient registries, etc.), not only to support health care delivery (the so-called primary use of data), but also for health research and health policy making (the so-called secondary use of data).

The system will revolve around adherence to the principles of transparency and protection of personal data of patients, on strengthening data portability, based on the provisions of Article 20 of the GDPR. The Commission will work together with member states to develop the European Health Data Space, the construction of which will revolve around three pillars:

1. A strong data governance system and a framework of data exchange rules;
2. Data quality;
3. Establishing a structure that can enable interoperability.

The Commission had already announced, in the European Data Strategy28 and in the more recent Data Governance Act[36], its intention to achieve concrete results in the area of health data and to exploit the potential created by developments in digital technologies to introduce innovation in health. The collection, access, storage, use and reuse of health data poses challenges that need to be addressed in a regulatory framework that best serves the interests and rights of citizens, particularly with regard to the processing of health status data.

Although the Cross-Border Healthcare Directive[37] created a collaborative framework among national authorities responsible for eHealth (the "eHealth Network"), existing agreements and tools provide and only partially address the challenges.

[34] Ibidem 8

[35] Regulation (EU) 2021/522 of the European Parliament and of the Council of March 24, 2021 establishing a programmen of Union action in the field of health for the period 2021-2027 ("EU Health Programme") (EU4Health) and repealing Regulation (EU) No. 282/2014.

[36] Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on the European data governance, COM(2020) 767 final.

[37] Directive 2011/24/EU of the European Parliament and of the Council of 9 March 2011 , on the application of the rights of patients concerning cross-border health care.

Failure to exchange health data has a negative impact on the delivery of health services (and thus on the primary use of health data). The level of digitization varies widely within each Member State, and interoperability among health service providers remains limited. The eHealth network-and the related IT infrastructure-has improved the cross-border exchange of health data for health care, especially with regard to patient records and e-prescriptions. However, its voluntary and non-binding nature has negatively affected its adoption and limited its impact.

Exercising access and control over one's health records is often extremely difficult for patients. Electronic health records (EHRs) are not yet a reality throughout the Union, and many patients cannot easily access and use the information they contain, or transfer it between different providers, especially when the transfer is cross-border. This leads to duplication of effort, inefficiencies, delays in care, and higher costs for health systems and patients. The sharing of EHRs is limited, which means that this information cannot be easily shared in the treatment of patients.

As for the secondary use of health data, access to and exchange of health data for scientific research and innovation, new policy-making and regulatory activities remains very limited within the Union.

The collection, access, storage, use, and reuse of health data in health care poses specific challenges, mainly legal and technological in nature. In fact, from a regulatory perspective, the GDPR establishes a common framework of rules to which member states have added additional specifications and restrictions in relation to the processing and sharing of healthcare data. Thus, the processing of personal health data in member states appears to be fragmented, leading to obstacles and limited access by researchers and public institutions, which in turn reduces the EU's competitiveness and innovation potential globally.

Member states have different approaches to accessing and sharing health data. Some member states have established national bodies that facilitate access to health data; however, such bodies do not exist in all member states. Limited cooperation, governance, and IT infrastructure at the EU level hinder access to health data by researchers, public institutions and regulatory bodies.

A growing number of digital health tools then integrate artificial intelligence (AI) systems. The Commission is already working on a horizontal framework for AI that covers security and fundamental rights aspects, which is intended to be applied in various sectors, including health products. However, specific health-related aspects that rely on the future AI framework, including training, testing, and validation of AI systems, as well as aspects not covered by this horizontal framework may require further consideration.

The use of AI tools, and in particular the opacity of some applications, may make it difficult to assign responsibility or ensure compliance. It is therefore important to ensure adequate safeguards on fundamental rights and damages.

All these issues should be analyzed and solved in the European Heath Data Space; in particular, the program aims to:

a. Ensure the access, sharing, and optimal use of health data for health care delivery, as well as its reuse for research and innovation, policy development, and regulatory activities, in a secure, timely, transparent, and reliable and with appropriate institutional governance;
b. Promote a true single digital health market, covering health services and products, including telemedicine, telemonitoring and mobile health;
c. Improve the development, deployment and application of digital health products and services that are reliable, including those incorporating artificial intelligence in the health sector;
d. Establish an appropriate legal and governance framework to cover access and exchange of health data for health care delivery, research, policymaking, and regulatory activities.

The European Health Data Space, integrated with aspects of the Data Governance Act, will provide for the designation of national digital health bodies and sectoral bodies to deal with the secondary use of health data. It will also include: support for public authorities (e.g., medical agencies, epidemiological institutions, National Institutes of Health, HTA bodies, EMA, ECDC) to access health data in full compliance with data protection rules; access to genetic data and linkage with health data; reuse of data held by private entities; and support for training and testing of AI health applications. The interaction with the GDPR, particularly Articles 9 and 89, regarding the regulation of health data will be the subject of detailed study and analysis.
Efforts will also be made toward eliminating technical barriers to the use and reuse of data, particularly those related to infrastructure, interoperability, data quality, and standards in healthcare. Options regarding infrastructure for the use of data for health care will be examined, building on the eHealth digital service infrastructure (MyHealth@EU) for cross-border exchange of patient data when traveling abroad. Options regarding enhanced interoperability of electronic health records, in line with the European exchange format, as well as semantic and technical interoperability of different types of data will be explored. Regarding data access for research, policymaking, and regulatory purposes, options will address different models of interoperable data access infrastructure and related services to facilitate secure and cross-border storage, processing and analysis of health data.

Medical Research: an enlightening opinion from the Italian Data Protection Authority

Avv. Silvia Stefanelli

One of the most complex issues after the GDPR becomes fully effective is undoubtedly that of scientific research in healthcare. There are several reasons for this.
The first, without a doubt, is a changed reality.
The increasing digitalisation of our society and especially of healthcare leads to a hyper production of data, paving the way for projects, initiatives, and analysis possibilities that were unimaginable until a few years ago. Thus the questions and doubts that arise from all stakeholders - be they healthcare facilities, scientific societies, industry, universities, individual healthcare professionals - are the most varied: how can I use the data collected for diagnosis and treatment for research? Can I provide third parties with data to train AI software? Whose result

is it? How can I build a DB of health data? Can I profile the data? How can I deal with so-called Reald Word Data? When can I consider a piece of data as anonymous? And these are just a few.

This 'new' - by now not so much - situation then falls into a legal framework of complex interpretation and application.

The arrival of the GDPR has been hailed as a breath of fresh air towards scientific research: Article 5(b) has introduced the possible processing of data for ulterior purposes (e.g. scientific research) when the same can be considered 'not incompatible' with the primary purpose (e.g. diagnosis and treatment), Article 6(4) has indicated the criteria for carrying out this compatibility test (in deference to Opinion no. 3/2013 of the Working Party), Article 6(3) has indicated the criteria for carrying out this compatibility test (in deference to Opinion no. 3/2013 of the Working Party), and Article 6(3) has indicated the criteria for carrying out this test (in deference to Opinion no. 3/2013 of the Working Party). 3/2013 of the Working Party), Art. 9(j) introduced an ad hoc legal basis for scientific research, Art. 14(5)(b) relieved the data controller of the obligation to provide information where this appears too complex, and Art. 89 indicated the specific safeguards to be applied in scientific research.

The picture, however, presented some shadows for the health area: the legislator of the GDPR in fact did not have the courage (more likely the political strength) to go all the way and, in Article 9(4), left the door open for Member States to 'maintain or introduce further conditions, including limitations, with regard to the processing of genetic data, biometric data, or data concerning health'.

In essence, 'throwing the stone and hiding the hand'.

This door then became a gateway that led Member States (some more, some less) to introduce very different rules, often very stringent.

An excellent comparative analysis can be found in the important EU work Assessment of the EU Member States' rules on health data in the light of GDPR - 2021) where the different disciplines in the various Member States are highlighted, and the difficulties therefore of carrying out research at a European level due to the differences in the processing of data. A Community response to this complex problem is currently being sought through the Proposal for a Regulation on the European Health Data Space (presented on 3 May 202) on which the EDPS and EDPS have already had the opportunity to express their views in a specific Joint Opinion published on 12 July 2022.

As far as Italy is concerned, it cannot be said that it has not (ab)used the space left by the GDPR for the introduction of specific rules for scientific research in the health field (the aforementioned Article 9(4)).

While I do not in fact want to deny the importance of protective rules in this area, the Italian result is undoubtedly - and I am certainly not the only one to say so - very stringent as well as a fair mess.

The D.Lgs 101/2018 harmonising our Privacy Code to the GDPR, betraying the spirit of the GDPR itself, has redone the make-up of the previous Article 110 and re-presented Article 110-bis, born as an ad hoc rule (according to our insane habits) through the European Law 2017 - Law no. 167 of 20 November 2017.

Very briefly.

- art. 110 concerns medical, biomedical and epidemiological research and (going beyond the EU provisions that spoke only of "further conditions") imposes consent as a legal basis, establishing that where it is not possible to collect the consent of the interested party, the opinion of the Ethics Committee and the Prior Consultation of the Guarantor ex art. 36 GDPR are required (obviously downstream of an Impact Assessment ex art. 35 GDPR) .
- Article 110-bis, on the other hand, deals with further processing by third parties, for which the authorisation of the Garante is required, to be issued within 45 days and whose silence is equivalent to refusal.

It is a pity, however, that the current data protection system no longer envisages an authorisation regime on the part of the Garante, and everyone is wondering whether or not the requirements set out in Measure 146 of 5 June 2019 (which 'ferried' the previous authorisations for the processing of sensitive data into the GDPR world) can be considered a general authorisation, compliance with which also allows processing by third parties.

In this decidedly complex (and somewhat confusing) framework, the Privacy Guarantor recently intervened with an opinion issued as part of a Prior Consultation pursuant to Article 110, clarifying some important aspects (Register of Measures No. 238 of 30 June 2022).
This opinion undoubtedly deserves to be analysed.

The Azienda Ospedaliera Universitaria Integrata di Verona submitted an application for Prior Consultation (pursuant to art. 110, paragraph 1, Privacy Code and art. 36 GDPR) as promoter of an interdepartmental, non-pharmacological observational study called "DB Torax" with both prospective and retrospective data.
Basically, the aim was to create a database of the population of patients suffering from neoplastic (and non-neoplastic) pathologies of the thoracic district, which could then be used, even at a later date, for further studies aimed at improving knowledge and clinical practice in the field of thoracic district pathologies: more precisely, the study protocol specified that 'Detailed statistical analysis plans will be set up in future research protocols that will use this database as a source of data in order to achieve the objectives [of] specific studies'.
The Company submitted, as an annex to the application, an Impact Assessment under Article 35 GDPR concerning the creation of the same database and subsequent studies.
Regarding the legal basis, the Impact Assessment showed that
- for prospective ones, consent would be obtained
- for the retrospective, since there was a lot of data referring to deceased persons and since the collection of consent was very complex even for the living (only 10% was available), the legal basis was to be found in the procedure of Article 110 of the Privacy Code

More precisely, then, data processing for subsequent studies was considered 'further' and 'not incompatible' with the initial collection, without the need for further legal bases.
The same Impact Assessment then explained precisely which information sets will be collected, how the data will be pseudonymised, how (in 20 years' time) the data will be rendered completely anonymous, and also the security measures implemented.
On this perspective, the Garante issued its opinion.

Regarding the legal basis of the processing, after a very precise and detailed reconstruction (really useful given the difficulties outlined above), the Garante makes some interesting considerations.

More precisely, he specifies that consent for prospective studies and the procedure under Article 110 of the Private Code for retrospective studies legitimise the processing of data for the purpose of building the database. On the contrary, subsequent studies, which will be carried out 'fishing' for data from the DB, cannot be considered compatible with the initial processing and will therefore require special consent.

More precisely, so it reads:

It follows that the consents collected for the creation of the Torax Database (or, alternatively, the prior consultation procedure under consideration) cannot also constitute the legal basis for further processing, since they represent a still partial manifestation of will that will be progressively completed with the further and specific requests for consent that will have to be made by the Company when carrying out future studies (cons. 50, art. 6 par. 4, of the Regulation and Guidelines 5/2020 on consent under Regulation (EU) 2016/679, cited above).

In essence: 'general' consent (or Article 110 procedure) for the establishment of the Database and specific 'progressive' consent (or Article 110 procedure) for the individual studies to follow.

Still very interesting is the analysis on the anonymisation of the data.

In fact, the Garante considered the techniques presented for this purpose to be valid, which provide for making the data anonymous:

- The elimination of 51 variables including those that lead to the direct identification of the interested parties ("record_id" and "patient code"), further variables that are excessive or likely to increase the risk of re-identification (e.g. date of birth, signature of informed consent), as well as those "useful more for the organisational purposes of the Study than for data analysis purposes".
- The randomisation of 57 variables into 3 categories: "value in years for age at enrolment ("age_at_enrollment") [...] age at diagnosis ("age_diagnosis"), and [...] days for the remaining variables in the section covering all dates reported in the Torax DB".
- The generalisation of 293 variables by means of aggregation and K-anonymisation consists of ensuring that each value concerning a data subject is shared by at least a minimum number (k) of other persons within the set.

The Garante considered the application of these techniques suitable for lowering the risk of re-identification to such an extent that the data could legitimately be considered anonymous.

At the end of the reading, I wondered what lessons we can draw from this opinion.

The first is undoubtedly that when the Impact Assessment is done well, the Guarantor is not an enemy but an organ (precisely) of consultation: in this sense, there is no reason to try to 'avoid' applying Article 110 of the Private Code. (a request that is instead often raised). Instead, there are reasons to try to understand the system and try to work well.

The second assessment (closely related to the first) concerns the fact that we may not like the 'system of Art. 110 and 110-bis' (I do not like it and I think it betrays the spirit of the GDPR), but this is what we have at the moment: therefore until a forthcoming intervention of our legislator (or perhaps a hawkishness of the Community legislator with the Health Data Space) our Guarantor cannot go beyond the stakes imposed by the legislator itself.

The third assessment concerns anonymous data, an issue on which there continues to be great fear (especially on the part of public facilities) of taking responsibility for when to consider them truly anonymous: we now have a clear, precise and scrutinised example from the Garante. So there are no more excuses.

Then, perhaps, in this opinion one could have been a little more courageous about the 'non incompatibility' of processing for subsequent studies, but the road from compatibility is still, even culturally, uphill. This is demonstrated by the constant postponement of the EDPB itself, which with every document tells us that it will tell us how to do it. We wait confidently.

Undoubtedly at the moment we are taking home a clear document on how to build a health database.

In view of the interpretative chaos, the hesitations and fears of the health structures, in my opinion this is no small thing.

The European Health Data Space. Overview of the main aspects of the proposed Regulation

Elisabetta Biasin

On May 3rd 2022, the European Commission put forward a legislative proposal on the European Health Data Space (EHDS).[38] The proposal addresses long-standing issues related to healthcare interoperability and patient empowerment within the European Union. It does so by laying down rules and mechanisms supporting the primary and **secondary use of electronic health data** and establishing a mandatory **cross-border infrastructure** enabling the primary and secondary use of electronic health data. It also aims at strengthening the **rights of natural persons** in relation to the availability and control of their electronic health data and lays down rules for the placing on the market, making available or putting into service of electronic health records systems (**EHR systems**) in the European Union (EU). [39]

The regulation is expected to apply to several actors in the data sharing landscape. It will apply to controllers and processors of electronic health data, including those established in third countries and data holders who will grant access to electronic health data by data users in the Union. Manufacturers and suppliers of EHR systems and wellness applications and the users of these products will be subject to the EHDS. Moreover, there will be **new actors in the data sharing landscape**, such as the health data access bodies and digital health authorities**. Health data access bodies** will have the role of facilitating the secondary use of electronic health data and ensuring that data holders and data users have access to electronic health data. Data holders will have to cooperate with health data access bodies to ensure the availability of electronic health data for data users. Every Member State will have to establish **digital health authorities**. In

[38] Commission, 'Proposal for a Regulation of the European Parliament and of the Council on the European Health Data Space' COM(2022) 197 final.

[39] EHDS proposal, art 1.

essence, they will be responsible for implementing and enforcing the EHDS rules on the national level.

The EHDS regulation will apply to **electronic health data**, which may consist of both personal and non-personal data. **Personal electronic health data** will encompass data concerning health as defined in the GDPR, personal data related to the physical or mental health of a natural person, including the provision of health care services which reveal information about their health status, personal data relating to the inherited or acquired genetic characteristics, as well as data determinants of health, such as behaviour, environmental, physical influences, medical care, social or educational factors.[40] **Non-personal electronic health data** will consist of 'data concerning health and genetic data in an electronic format that falls outside the definition of personal data' as in Article 4 of the GDPR.[41] Electronic health data will also concern **inferred and derived data,** which are exemplified by the proposal as 'diagnostics, tests and medical examinations, as well as data, observed and recorded by automated means'.[42]

The EHDS proposal includes rules on the **primary use of electronic health data,** which are contained in its Chapter II. The primary use of electronic health data is defined as the 'processing of personal electronic health data for the provision of health services to assess, maintain or restore the state of health of the natural person to whom that data relates'.[43] The EHDS proposal sets **rights for individuals** for personal electronic health data, stemming from the right to access to the right to receive an electronic copy of their electronic health data.[44] Article 5 of the proposal envisages that the Member States could establish electronic health data access services enabling the exercise of the mentioned rights, or they could establish proxy services enabling a natural person to authorize other persons to access their electronic health data on their behalf.[45] Article 4 of the proposal establishes that **health professionals** shall have access to the electronic health data of natural persons under their treatment, and shall ensure that the personal electronic data they treat are updated with information related to the health services provided.

The EHDS proposal establishes **priority categories of personal electronic health data for primary use.**[46] Where data is supposed to be processed in electronic format, the Member States will have to implement access to and exchange of personal electronic health data for primary use for some categories, encompassing patient summaries, electronic prescriptions, electronic dispensations, medical images and image reports, laboratory results, discharge reports.[47] The European Commission will have to lay down with implementing acts the technical specification

[40] For further exemplifications of what the EHDS proposal considers as personal electronic health data, see EHDS proposal, Recital 5.
[41] EHDS proposal, art 2(2)(b).
[42] EHDS proposal, rec 5.
[43] EHDS proposal, art 2(2)(d).
[44] EHDS proposal, art 3. For an overview on the EHDS, Data Act, and data portability, see Charlotte Ducuing and others, 'White Paper on the Data Act Proposal' [2022] SSRN Electronic Journal 28 <https://www.ssrn.com/abstract=4259428> accessed 17 November 2022.
[45] EHDS proposal, art3(5).
[46] EHDS proposal, art 5.
[47] The details of these categories are further substantiated in Annex I of the EHDS proposal.

for such categories of data, setting out the **European electronic health record exchange format.**[48]

Chapter V of the EHDS proposal deals with the **secondary use of electronic health data.** According to the proposal, constitutes secondary use of electronic health data the processing of electronic health data for purposes set out in Article 34 of the Regulation.[49] As per the same article, health data access bodies will have to provide access to certain kinds of electronic health data[50] where the intended purpose of the processing pursued by the applicant complies with one of the following **purposes**:

a) activities for reasons of public and occupational health;
b) to support public sector bodies or Union institutions, agencies and bodies, including regulatory authorities, in the health or care sector to carry out their tasks defined in their mandates;
c) to produce national, multi-national and Union level official statistics related to health or care sectors;
d) education or teaching activities in health or care sectors; (e) scientific research related to health or care sectors;
e) development and innovation activities for products or services contributing to public health or social security or ensuring high levels of quality and safety of healthcare, of medicinal products or of medical devices;
f) development and innovation activities for products or services contributing to public health or social security, or ensuring high levels of quality and safety of health care, of medicinal products or of medical devices;
g) training, testing and evaluating of algorithms, including in medical devices, AI systems and digital health applications, contributing to the public health or social security, or ensuring high levels of quality and safety of health care, of medicinal products or of medical devices;
h) providing personalised healthcare consisting in assessing, maintaining or restoring the state of health of natural persons, based on the health data of other natural persons.[51]

The EHDS proposal establishes so-called **minimum categories** data holders shall make available for secondary use. These are enlisted under **Article 33** of the proposal and consist in the following:

a) Electronic Health Records (EHRs);
b) data impacting on health, including social, environmental behavioural determinants of health;
c) relevant pathogen genomic data, impacting on human health;
d) health-related administrative data, including claims and reimbursement data;
e) human genetic, genomic and proteomic data;

[48] EHDS proposal, art 6.
[49] EHDS proposal, art 2(2)(e).
[50] These are enumerated under article 33 of the proposal, see *infra*.
[51] EHDS proposal, art 34.

f) person generated electronic health data, including medical devices, wellness applications or other digital health applications
g) identification data related to health professionals involved in the treatment of a natural person;
h) population wide health data registries (public health registries);
i) electronic health data from medical registries for specific diseases;
j) electronic health data from clinical trials;
k) electronic health data from medical devices and from registries for medicinal products and medical devices;
l) research cohorts, questionnaires and surveys related to health;
m) electronic health data from biobanks and dedicated databases;
n) electronic data related to insurance status, professional status, education, lifestyle, wellness and behaviour data relevant to health;
o) electronic health data containing various improvements such as correction, annotation, enrichment received by the data holder following a processing based on a data permit.

The proposal **prohibits certain purposes for secondary use** of electronic health data. Purposes such as taking decisions detrimental to a natural person based on their electronic health data; taking decisions in relation to a person or a group thereof to exclude them from the benefit of an insurance contract or to modify their contributions and insurance premiums; advertising or marketing activities, developing products or services that may harm individuals and societies at large shall be prohibited.[52]

There are **mechanisms and governance requirements** for the secondary use of electronic health data. As anticipated *supra,* the Member States will have to designate health data access bodies, which will have the role – *inter alia* – to decide on data access applications, and authorise and issue data permits.[53] The **data permit** will be the administrative decision issued to a data user by a health data access body or data holder to process the electronic health data.[54] To obtain a data permit, a natural or legal person shall submit a **data access application** containing the elements enlisted under Article 45 of the EHDS proposal. Data access bodies will be responsible for granting access to electronic health data for secondary use.[55] As part of their tasks, they will have to gather and compile or provide access to the necessary electronic health data from various data holders and put those data at the disposal of data users in a **secure processing environment**.[56] Health data access bodies shall take security measures for secure processing

[52] See EHDS proposal, art 35.
[53] EHDS proposal, art 37.
[54] EHDS proposal, art 2(2)aa.
[55] EHDS proposal, art 36(1).
[56] EHDS proposal, art 37(g). The definition of a 'secure processing environment' is given by the Data Governance Act , and it "means the physical or virtual environment and organisational means to ensure compliance with Union law, such as Regulation (EU) 2016/679, in particular with regard to data subjects' rights, intellectual property rights, and commercial and statistical confidentiality, integrity and accessibility, as well as with applicable national law, and to allow the entity providing the secure processing environment to determine and supervise all data processing actions, including the display, storage, download and export of data and the calculation of derivative data through computational algorithms". Data Governance Act, art 2(20), Regulation (EU) 2022/868 of the European Parliament and of the Council of 30 May 2022 on European data governance and amending Regulation (EU) 2018/1724 (Data Governance Act) [2022] OJ L152/1.

environments, including access restrictions, access logs, and risk minimisation measures for unauthorised data processing.[57]

Another important aspect concerns **health data quality and utility for secondary use**. To face the long-standing challenges on data quality and interoperability in healthcare, the proposed Regulation offers some rules to bridge these gaps. Datasets made available through health data access bodies may have a Union **data quality and utility label** provided by the data holders.[58] These will be mandatory should the datasets be collected and processed with the support of Union or national public funding. Furthermore, the Commission will be called to establish an EU Datasets Catalogue, and by means of implementing acts, it may determine the minimum specifications for cross-border datasets for secondary use of electronic health data.[59] Moreover, health data access bodies will have to inform the data users about the available datasets and their characteristics through a metadata catalogue, including information about, e.g. source, scope, characteristics and conditions for making electronic health data available.[60]

In addition to the rules on the primary and secondary use of electronic health data, the EHDS proposal contains requirements for **EHR systems** and wellness apps**.** EHR systems are defined as 'any appliance or software intended by the manufacturer to be used for storing, intermediating, importing, exporting, converting, editing or viewing electronic health records'.[61] To place EHR systems on the market or put them into service, manufacturers of EHR systems will have to, among other things, ensure the systems are in conformity with some essential requirements, provide technical documentation and instructions for use, affix the CE marking, and register their systems.[62] The **essential requirements** are contained in the proposal's Annex II and include general safety and performance requirements and more specific requirements on **interoperability, safety and security.**[63]

The proposal also covers **wellness applications**, defined as 'any appliance or software intended by the manufacturer to be used by a natural person for processing electronic health data for purposes other than health care, such as well-being and pursuing healthy lifestyles'.[64] Manufacturers of wellness applications claiming interoperability with EHR systems may voluntarily label their products.[65] The label would indicate that these comply with the EHDS requirements on interoperability. Article 32 of the proposal mandates the Commission to create a publicly accessible **database** with information about certified EHR systems and wellness applications.

Finally, the proposed regulation sets rules for **European governance and coordination,** to reduce the risks of fragmentation across the Union**.** The **EHDS Board** will be established to

[57] EHDS proposal, art 50.
[58] EHDS proposal, art 56.
[59] EHDS proposal, arts 57-58.
[60] EHDS proposal, art 55.
[61] EHDS proposal, art 2(2)(n), whereby EHRs are a 'collection of electronic health data related to a natural person and collected in the health system, processed for healthcare purposes' (EHDS proposal, art 2(2)(m)).
[62] EHDS proposal, art 17.
[63] EHDS proposal, Annex II.
[64] EHDS proposal, art 2(o).
[65] EHDS proposal, art 31.

facilitate cooperation and the exchange of information among Member States. It may issue written contributions and exchange best practices, share information concerning risks posed by EHR systems, and facilitate the exchange of views on the primary and secondary use of electronic health data with the relevant stakeholders.[66] In doing so, the EHDS Board will have the role of fostering coordination with the Member States and ensuring the cooperation among digital health authorities.

Data lake in healthcare: improving research/care through data concentration

Daniele Panfilo

The ability to aggregate information into systems that allow for quick and easy access and reuse, such as data lakes or data warehouses, is one of the key drivers for research and development of data analytics-based solutions. This is even clearer in the case of health data. This has been further underscored by the current pandemic that has made the need for an infrastructure capable of facilitating the sharing, access and safe reuse of health data imperative.
While the exponential growth of available information follows a very high rate of growth due to the significant development and subsequent deployment of data acquisition devices, the access and reuse of the information asset shows very different growth factors quite different.

The causes hindering a broader democratization of health information, aimed at encouraging the rapid implementation of research and development projects, are varied and have different origins.
On the one hand, the lack of a standard platform for secure sharing of health data, and on the other hand, the sensitive nature of the data processed constitute some of the main factors behind the poor reuse of the information asset.
While The European Monitoring Tool[67] predicts that by 2025 the European data market will reach the value of more than 140 billion euros, it is clear that a real paradigm shift in technology will be necessary for the valorization of the information asset to take place as expected.
To this end, several European initiatives have emerged and are emerging, with the goal of enabling access to and reuse of health information assets through aggregation in data lakes or data warehouses. One example of such initiatives is provided by the eHealth platform Belgium, a Belgian government service, which offers the chance for actors in the health care landscape to securely exchange even sensitive information. Another case is that represented by the UK's The Health Data Research Hubs, which facilitates access to national health system data for the public, academic, and industrial research sectors in the United Kingdom.
The emergence of such hubs in several member states shows how central the issue of data sharing is and how this need is felt throughout the member states of the union.

[66] EHDS proposal, ch VI.

[67] First Report on Facts and Figures Updating the European Data Market Study Monitoring Tool By International Data Corporation (IDC) and the Lisbon Council, European Data Market Study Updated SMART 2016/0063.

The aggregation of such information through dedicated platforms not only stimulates research by facilitating access to data, but also enables the elimination of geographic barriers, encouraging the emergence of international collaborations and synergies-the lifeblood of scientific progress.
For the European data market forecasts to be realized, and for the European Union to fully benefit from the strategies presented in the report "Impact Assessment on enhancing the use of data in Europe," it is necessary that the technologies available to the IT world, and the search for innovative data privacy solutions, develop and be adopted in a synergistic manner.

Organizational Tools: partnerships, consortia, contracts

Paolo Bartoli, Ruggero Di Maulo

Registries supporting observational studies of rare diseases are important tools for a strategy aimed at accelerating medical research and the development of new therapies and solutions to improve patients' quality of life.

The involvement of patients through their Associations therefore plays an increasingly central, in fact it is now clear that these are at the heart of the entire implementation process and have briefly some key prerogatives, such as:

- They are the stakeholders with respect to the ultimate goal (new therapies or solutions);
- They guard the instrument and the data collection;
- They are guarantors of the interests of the community for which they work;
- They are vehicles for engagement and sharing with participants, both physicians/researchers and patients.

The particular nature of registries in the head of an Association requires the ability to structure and maintain operational capacity over time, to engage patients and physicians, and to collect data while ensuring its security and availability. Such data are of increasing value to the ecosystem as they are the basis for the generation of real-world evidence (RWE), which is increasingly required by regulators and companies in both the early stages of drug research and subsequent registration, pricing, and post-marketing surveillance activities.

These elements rely on "industrial" and administrative management capacity, the greater the underlying technological and regulatory complexity of a registry that wants to survive over time and be in compliance with legal regulations. Therefore, economic and human resources are required that are not easy to obtain and maintain over time.

Such management capacity cannot be provided outside of an enterprise approach. The structured organization of human and material resources for a defined purpose offers these guarantees, provided it can sustain itself financially. Preparation and experience, safety, quality are actors that have a high cost, and must come together in a model where roles and responsibilities are clear.

Another key aspect is an approach aimed at the medium to long term, as it is not uncommon in this context for research results to lead to concrete solutions for subsequent generations of patients who have participated in the early-stage research. A "project-based" approach, with teams organized on an extemporaneous basis and timelines of 1 to 3 years is effective for a clinical product trial, for example, but not so for a long-term observational study, where a permanent organization for data quality collection and management on the one hand, and for patient and clinician engagement on the other, must be implemented.
Also from the point of view of economic sustainability, for a 1-3 year project a grant may be a suitable tool, whereas for a long-term observational registry, funds must be secured funds in a structural way (industry model).

Cloud-R aims to structure processes and make them organizationally and technologically operational by applying a proven industrialization model, and most importantly, it can finance from the beginning the implementation and maintenance of the registry. However, this capacity is possible if, and only if - having achieved the goal of quality data collection - these data, through their proper anonymization, can then be shared for secondary research purposes with other researchers and industries, for a fee, to remunerate the cloud-R business activity, a necessary condition to sustain the system in the medium to long term.

In the practice, the ability to bear the costs of the registry for the benefit of the Association and researchers is based on Cloud-R's ability to bear the business risk of registry implementation due to the exclusive availability of the anonymized registry data and the consequent ability to create, organize, and share such data for secondary research purposes, thus remunerating its investment.

The sharing of secondary data for Cloud-R has business value, based on an ethical purpose that is summed up in making knowledge and information available to other stakeholders even outside the single context in which the data are collected (see EMA recommendations) and at the same time to raise new financial resources, which are not available today for such independent research.

For its part, the Association is free to use the registry data for the primary purposes of research, typically on a non-profit basis, and in accordance with physicians' plans as outlined in the observational study protocol served by the registry. These are activities within the powers of the Association, for which it must nonetheless equip itself with the governing bodies and the minimum essential legal, administrative and regulatory expertise.

It is therefore important to mutually recognize the clear distinction between the nonprofit activities for-profit activities that gravitate to the Association and business activities characterized by the necessity inescapable financial balance and risk remuneration in the hands of Cloud-R.

- Primary research purposes: not-for-profit:
  - Association
  - Medical Doctors

The Association works in collaboration with physicians and referral centers by regulating relationships through agreements signed with the health facilities where the physicians work, and which implement what is stated in the protocol for aspects related to data collection and its use for publications and in general for primary uses.

- Secondary research purposes: for profit and social impact
  - Cloud-R

Extended knowledge sharing based on anonymized data, financial balance and risk reward.

The Association uses Cloud-R for all IT and technical activities as well as compliance aspects (from privacy to both process and facility security) for the purposes of data collection and registry management.

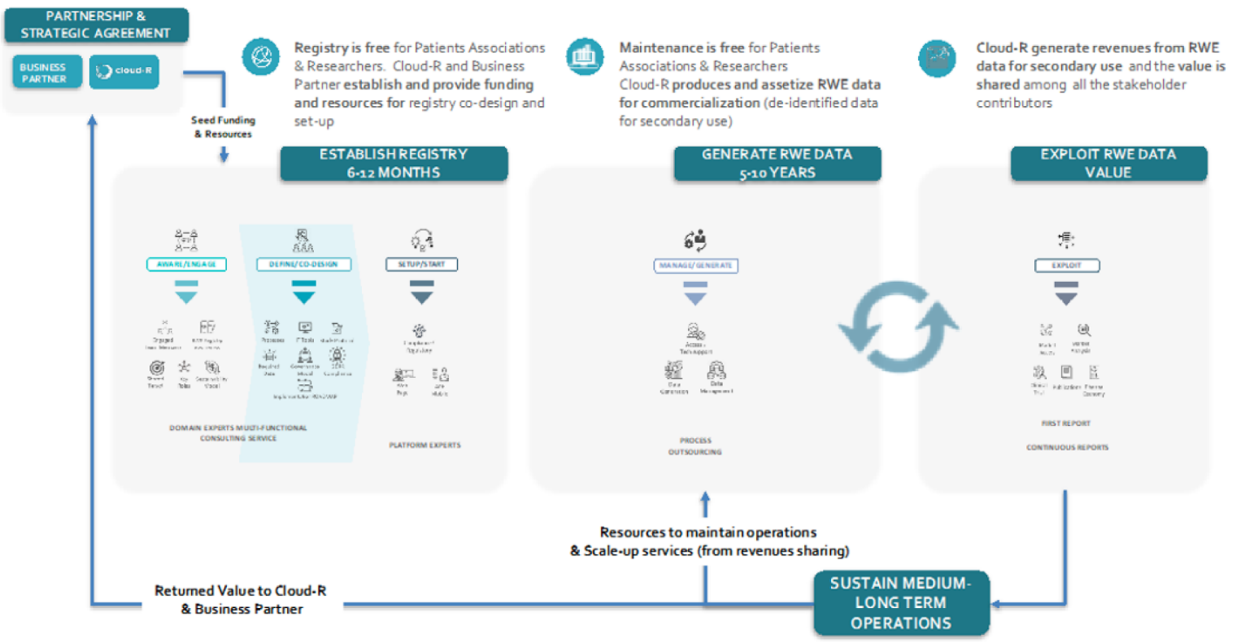
Cloud-R's ability to have the data anonymized allows the supply chain to be covered for both structure and process IT costs, as well as potentially covering all data entry and data monitor costs, which are usually covered by the participating centers and the promoter and allows the registry to be maintained in the medium to long term.

This distinction responds well to the different nature of the Association and Cloud-R, and corresponds to their respective corporate purposes.

The above premises form the basis of the fundamental clauses of the service contract underlying the implementation of the registry, and are signed by Cloud-R and the Association, which , as a rule, is the Promoter of the observational study.

The model can be viewed in its entirety through the following infographic:

Cloud-R CIRCULAR MODEL FOR LONG-TERM REGISTRY SUSTAINABILITY

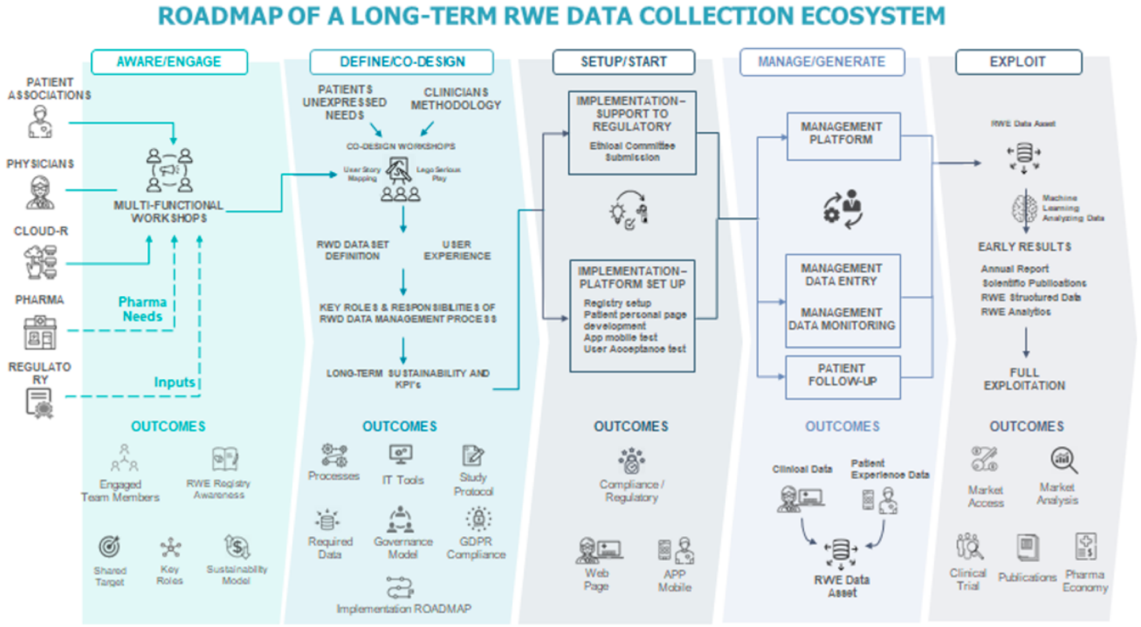

PARTNERSHIP & STRATEGIC AGREEMENT
BUSINESS PARTNER
cloud-R
Seed Funding & Resources
ESTABLISH REGISTRY 6-12 MONTHS
AWARE/ENGAGE
DEFINE/CO-DESIGN
SETUP/START
Processes
IT Tools
Required Data
Governance Model
Implementation ROADMAP
DOMAIN EXPERTS MULTI-FUNCTIONAL CONSULTING SERVICE
PLATFORM EXPERTS
GENERATE RWE DATA 5-10 YEARS
MANAGE/GENERATE
Data Management
PROCESS OUTSOURCING
EXPLOIT RWE DATA VALUE
EXPLOIT
Publications
FIRST REPORT
CONTINUOUS REPORTS
Resources to maintain operations & Scale-up services (from revenues sharing)
Returned Value to Cloud-R & Business Partner
SUSTAIN MEDIUM-LONG TERM OPERATIONS

Registry is free for Patients Associations & Researchers. Cloud-R and Business Partner **establish and provide funding and resources for** registry co-design and set-up

Maintenance is free for Patients Associations & Researchers
Cloud-R **produces and assetize RWE data for commercialization** (de-identified data for secondary use)

Cloud-R generate revenues from RWE data for secondary use and the **value is shared** among all the stakeholder contributors

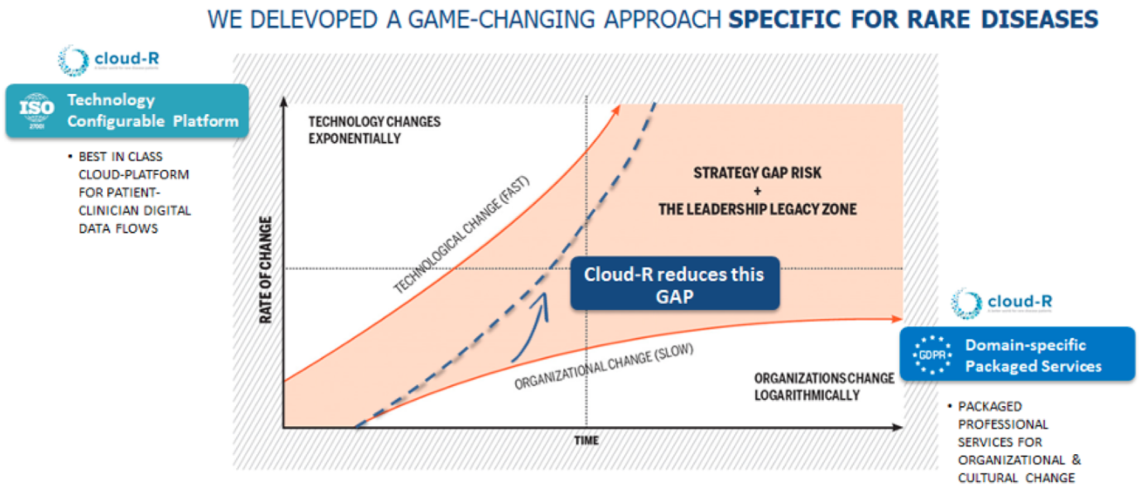
The generation of usable data for the market can be seen in more detail in this infographic:



RWE data in the case of rare diseases: how to extract new value from it

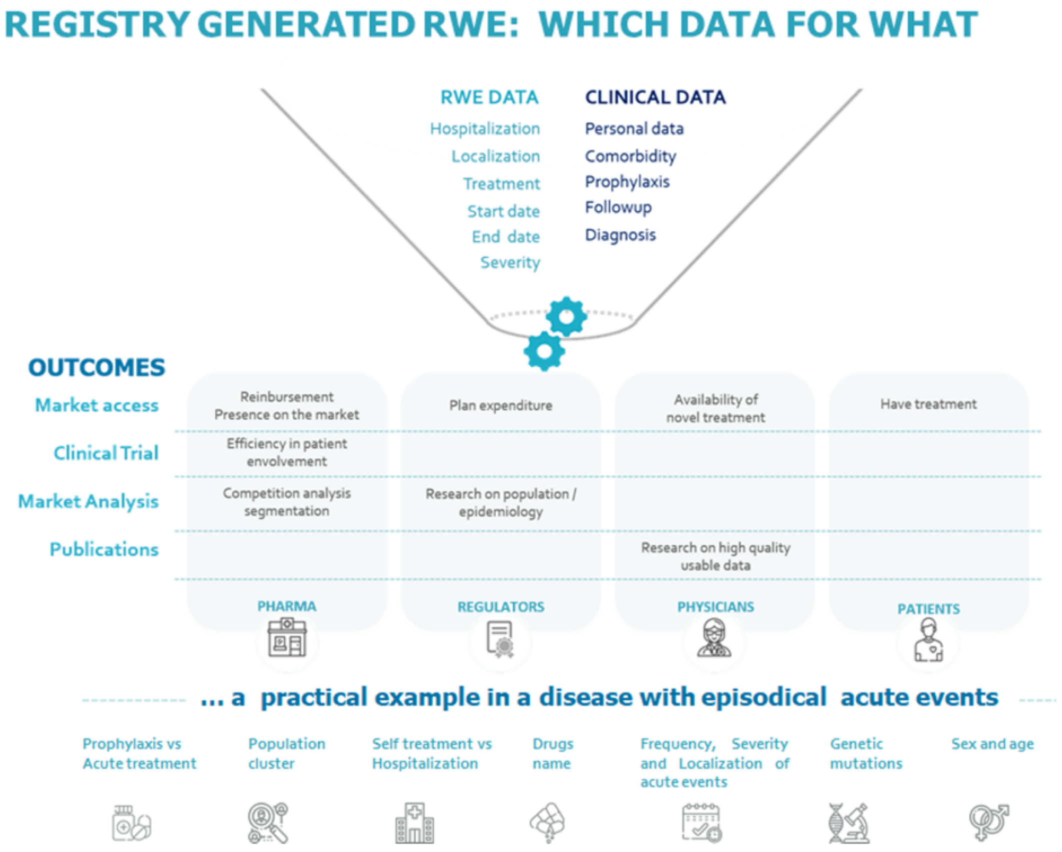
Paolo Bartoli, Ruggero Di Maulo

The model that is being carried out by Cloud-R has the capacity to revolutionize data collection in rare diseases. In fact, it intervenes on the governance phase of processes that are traditionally managed in an unstructured way, not integrated with the technological and IT phases, thus creating the breaking points that often then manifest themselves in the defaults under the compliance profile, in the unavailability of data and in the dissolution of the study organization itself. The real weakness of these projects lies in the different speed between the technological and organizational evolution - the human factor - processes, between the hard and soft parts of the necessary skills/culture and attitudes, which instead must be harmonized to lead to lasting results.


WE DELEVOPED A GAME-CHANGING APPROACH SPECIFIC FOR RARE DISEASES
cloud-R
ISO Technology Configurable Platform
• BEST IN CLASS CLOUD-PLATFORM FOR PATIENT-CLINICIAN DIGITAL DATA FLOWS
TECHNOLOGY CHANGES EXPONENTIALLY
TECHNOLOGICAL CHANGE (FAST)
STRATEGY GAP RISK
+
THE LEADERSHIP LEGACY ZONE
Cloud-R reduces this GAP
RATE OF CHANGE
ORGANIZATIONAL CHANGE (SLOW)
ORGANIZATIONS CHANGE LOGARITHMICALLY
TIME
cloud-R
GDPR Domain-specific Packaged Services
• PACKAGED PROFESSIONAL SERVICES FOR ORGANIZATIONAL & CULTURAL CHANGE

The focus of Cloud-R's action is therefore in cultural change, in the development of a collective self-awareness - mindfulness with a term in vogue today - of the stakeholders of the entire ecosystem, who never more than now are called upon to seize the opportunities given by the power of digital while at the same time managing the growing complexities that come with digitization.

The use cases can be many, such as:


REGISTRY GENERATED RWE: WHICH DATA FOR WHAT
RWE DATA
Hospitalization
Localization
Treatment
Start date
End date
Severity
CLINICAL DATA
Personal data
Comorbidity
Prophylaxis
Followup
Diagnosis
... a practical example in a disease with episodical acute events
Prophylaxis vs Acute treatment
Population cluster
Self treatment vs Hospitalization
Drugs name
Frequency, Severity and Localization of acute events
Genetic mutations
Sex and age

OUTCOMES	PHARMA	REGULATORS	PHYSICIANS	PATIENTS
Market access	Reinbursement Presence on the market	Plan expenditure	Availability of novel treatment	Have treatment
Clinical Trial	Efficiency in patient envolvement			
Market Analysis	Competition analysis segmentation	Research on population / epidemiology		
Publications			Research on high quality usable data	

Technologies for anonymization

The choice of technologies for anonymization

Daniele Panfilo

Access to and reuse of health data are often hindered by various factors. A major cause of difficulty is the fact that many of the health data are classified as sensitive data. The personal information contained within this data, if improperly disclosed, could cause a serious breach of the right to privacy. The risks associated with the use of health information also impact various dimensions from security to reputational. This requires that the person in charge of managing the health information asset adhere to the highest standards aimed at protecting the privacy of individuals. This will go a long way toward encouraging research and innovation while ensuring the security and rights of individuals.

From a technical perspective, there are several approaches to protecting the privacy of individuals ranging from standard anonymization and pseudo-anonymization solutions to modern data synthesization. The choice of one or the other technique depends on the degree of security one desired to achieve and the type of intended use for the data.

- **Anonymization:**
  Anonymization is that process of data obfuscation that irreversibly involves the total removal of the identifying element.
  There are multiple anonymization techniques, and a first macro distinction is between randomization and generalization techniques.

  - **Randomization:** operates on the degree of truth of the data to undermine the correlation that exists between the same and the person. The main randomization techniques fall under:

    - <u>Noise addition:</u> you go to add noise on certain columns with the goal of decreasing the accuracy of the information while still trying to keep the distribution unchanged.
    - <u>Permutation:</u> this is done by mixing the values of some attributes so that they turn out to be related to different people or entities. However, if there are strong logical relationships between some attributes the effect could be easily reversed (example treating physician and hospital department). This operation aims to break certain correlations between attributes that would facilitate identification of subjects. Nevertheless, this technique ensures that the marginal distributions of the attributes remain unchanged.

- Differential privacy: this technique is in principle similar to noise addition. The main difference lies in the fact that the latter involves "a priori" noise insertion. In contrast in differential privacy, the addition of noise occurs "on the fly" at the time of the execution of the database query. Thus, the query result has an appropriate amount of noise and can be shared with third parties since, if properly implemented, this technique does not allow easy re-identification of subjects. However, the true data remains available to the data controller.

- **Generalization/Aggregation:** aims to group individual records into classes containing multiple subjects to eliminate the possibility of point identification. This can be achieved by changing the scale of an attribute. For example, if we had a city column we could replace it with region by enlarging/diluting the information by enlarging the search set.

  - K-anonymity: Generalization techniques ensure the anonymity of people through their grouping into sets with other k-people. The idea behind k-anonymity techniques is to replace the point value of identifiers with ranges of values that include at least other k-subjects. For example, one replaces precise dosage values of a drug with ranges of ranges of values.
  - L-diversity/T-vicinity: extends and improves k-anonymity by requiring that within each value range with k subjects there exist at least L-different values. Strengthens the concept of k-anonymity against attacks by inference.

- **Pseudoanonymization:**

Pseudonymization aims to replace the identifying attributes of a piece of data with other values that do not allow for subject identification.
Thus, the goal of pseudonymization is to reduce the possibility of correlation of a data set to the original identity of the data subjects. Such data transformation, unlike the case of anonymization, is often a reversible process.
In essence, it is done by separating the data into direct identifiers (e.g., Social Security number) that allow easy identification of the subject, and which must be encrypted or masked, and indirect identifiers (e.g., place of birth) that can be shared instead without pre-processing steps.
The main pseudonymization techniques include:

- **Hashing functions:** this is a noninvertible function that takes as input an attribute of arbitrary length and returns a string of predefined length. Although it is not invertible, if the nature of the input attribute is known and if it has a finite size(e.g., acronyms of Italian provinces), the function allows the hashing result to be reproduced by simply leaving the input again.

- **Hashing functions and salt:** is an improved version of the classic hashing function that to limit the possible reidentification of subjects adds to the original input data a random value called salt that can be known.
- **Hash encrypted with stored key:** very similar to hash with salt. In this case the salt is a private key known only to the controller.
- **Secret key encryption:** is a reversible operation in which the original data is transformed using encryption techniques based on secret keys secret keys.
  The main distinction in pseudo-anonymization techniques is between. symmetrical and asymmetrical pseudo-anonymization:
  - Symmetric: in this case, the encryption and decryption key coincide;
  - Asymmetric: in this case, one key is used to encrypt and another separate key is used to decrypt the data, making it unnecessary to share the encryption key.
- **Tokenization:** involves assigning a randomly generated value to each instance of the attribute we intend to pseudonymize. Obviously, the mapping must take care that random numbers are not assigned same to different instances to avoid confusion.

- **Synthesization:**

Unlike previous anonymization and pseudonymization techniques, modern data synthesization solutions based on generative machine learning models represent an entirely new paradigm for personal data management.
These techniques assume that in most cases and applications, the individual record constitutes solely a liability while the real asset is the statistical content of the dataset.
Data synthesization by means of AI systems represents the new frontier in sensitive data management.
Modern synthetic data generation systems are tools capable of sampling new records from the input data distribution thus generating new data (synthetic).

Data generated through advanced artificial intelligence solutions are highly representative of the input statistical distribution, such that they can be used for training machine learning models or descriptive statistical analysis by exhibiting results that are statistically comparable to those obtainable with real data.

Given the artificial nature of the synthetic data obtained through generative models, the identification of real subjects or the possibility of Membership Inference Attacks (MIAs), in the absence of access to the parameters of the generating model or the real dataset and except for degenerate cases (datasets containing only a few units), is unlikely and much more complex when compared to the case of MIA on discriminative models[68].

Aindo and synthetic data

Daniele Panfilo

Aindo Ltd. has developed a technology based generative machine learning models for producing synthetic data in a healthcare context. This technology starting from real patients enables the creation of artificial patients that exhibit the same statistical characteristics as the real population. The artificial patient, generated by means of AI models, exhibits the statistical characteristics of the real one, thus maintaining utility in analysis but preventing the reidentification of real subjects or the sharing of personal information.
The synthetic patients generated can be used for statistical analysis or training of machine learning models without ever exposing the actual data. Such technology is intended to facilitate medical research and development projects by greatly speeding up data access time by allowing sharing of the statistical asset without compromising patient privacy.

The choice of dataset: primary scientific stage, feasibility, stage of definition for secondary use.

Paolo Bartoli, Ruggero Di Maulo

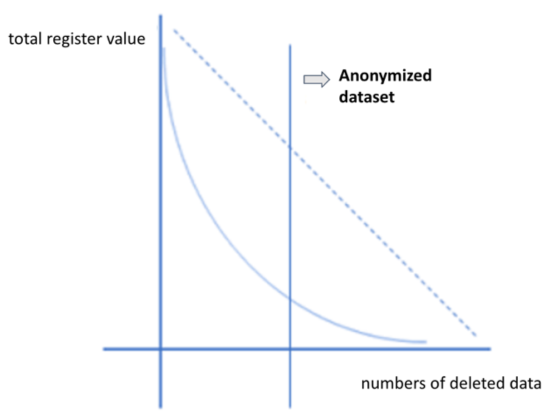
Datasets are defined by the study sponsor, with IT, cloud-R process, as well as regulatory/legal advice if needed.

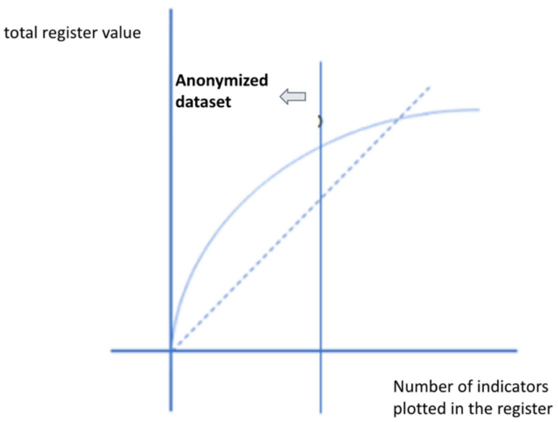
The anonymization techniques can be defined by the promoter as owner, or approved by it when proposed by cloud-R, which has the role of Data Processor and will have, by contract, the rights to use such anonymized data.

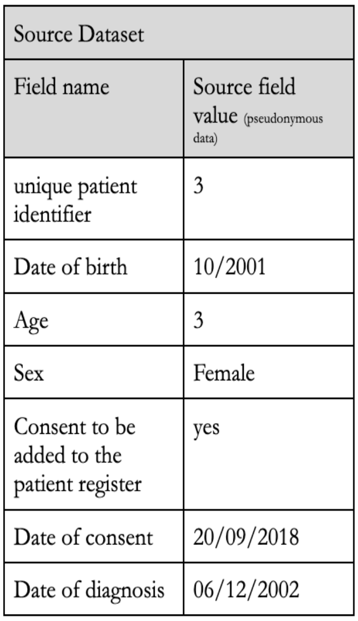
The parties' interests are consistent with each other and have the same functional goal: to make the data an autonomous object, devoid of reference to individuals.

The limited amount of data on rare diseases (few patients) makes the choice of anonymization techniques difficult. One of these involves deletion of items that could lead to re-identification of the patient. The more data that are deleted or merged, the more difficult it is to to trace the patient's identity, the less information there will be.

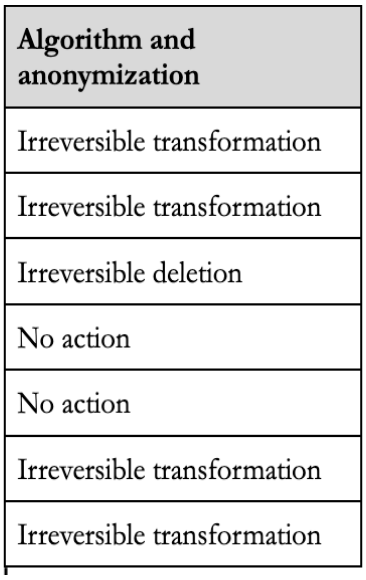
[68] "An Overview of Privacy in Machine Learning." https://arxiv.org/abs/2005.08679. Accessed 17 Jun. 2021.



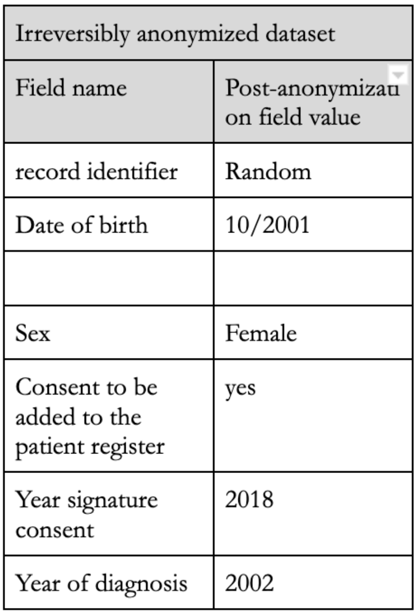




Source Dataset	
Field name	Source field value (pseudonymous data)
unique patient identifier	3
Date of birth	10/2001
Age	3
Sex	Female
Consent to be added to the patient register	yes
Date of consent	20/09/2018
Date of diagnosis	06/12/2002



Algorithm and anonymization
Irreversible transformation
Irreversible transformation
Irreversible deletion
No action
No action
Irreversible transformation
Irreversible transformation



Irreversibly anonymized dataset	
Field name	Post-anonymizau on field value
record identifier	Random
Date of birth	10/2001
Sex	Female
Consent to be added to the patient register	yes
Year signature consent	2018
Year of diagnosis	2002

There are several techniques that can be adopted, but they all pose the trade-off between data quality and anonymization, taking into account that the latter is not gradable. In addition, it may be necessary to consider the characters that define a piece of data as "anonymous." These could change due to digital technological evolution and AI, potential elements that could make recognizable tomorrow personal profiles underlying data now considered anonymous.
The possibility of bringing the dataset to a state of "essential" non relation to the concept of personal data can be experienced

with the adoption of algorithms that generate a dataset - derived from the original - defined as synthetic, in which granular data are transformed into information entities different from the original, while retaining the ability to generate statistics superimposed on those generated by the source dataset containing personal references. This topic is the subject of discussion elsewhere.

Example of reference software architecture

Alexandru Raileanu

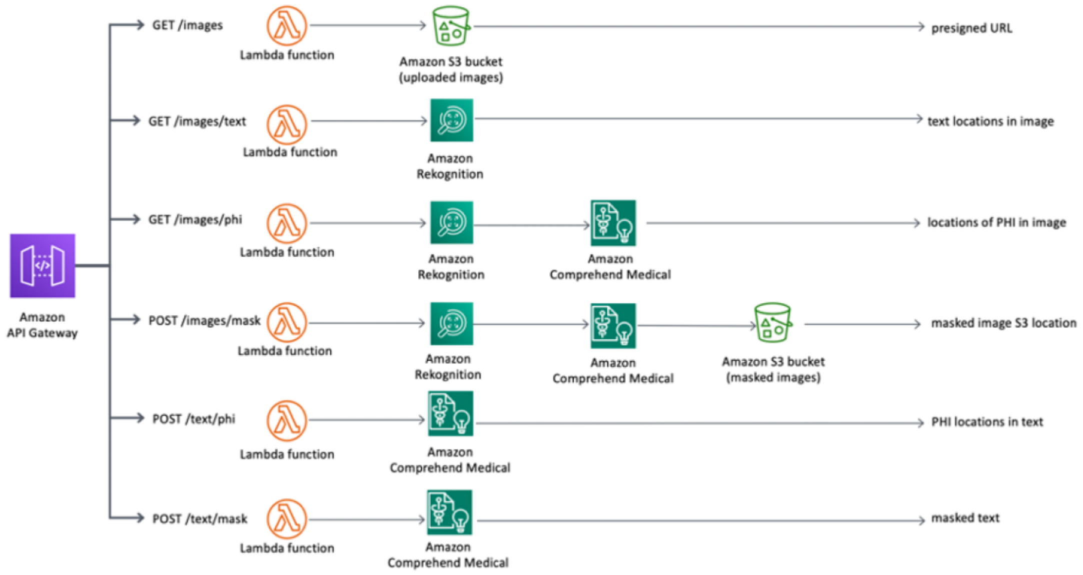
Healthcare and Life Science organizations generate large amounts of medical data such as RX or MRI images or patient information that are exchanged among various Software applications. A very common challenge for both medical personnel and developers designing systems to manage sensitive medical data is sharing data but at the same time complying with industry compliance rules (e.g., GDPR, PHI).

The solution presented below is an example of data masking architecture from which one can take a cue to build a more complex system customized to the needs of the case.

Microservices, which are nothing more than a paradigm for optimizing resources from a computational and cost perspective, provide for the creation of the functional logic for managing pre-processing, configuration, identification and finally for masking patient data.

The microservices interact with the managed Amazon Recognition service to identify text in an uploaded medical image and with Amazon Comprehend Medical to identify potentially sensitive information in the texts.

In addition, the template configures an Amazon Simple Storage Service bucket (flexible storage space) to store raw data and processed images, AWS CloudTrail to track data access (text or images), and Amazon CloudWatch logs for operational management. By default, the logs are encrypted, using the HTTPS protocol.



Conclusions and future prospects

The publication of the white paper "E-health Data Sharing" marks the conclusion of the first phase of a journey and the starting point for building a multi-stakeholder discussion, involving institutions, academia and the private sector. More specifically, as Data Valley we will continue to collect and integrate new contributions to enrich the first version of the white paper and create complementary tools to this document, such as checklists and toolkits, so to highlight the most relevant elements.

We invite those interested in sharing further experiences and models for data sharing in the health sector to write to us at info@datavalley.it