Beyond One Million Genomes

D6.10

Report on sustainability design and funding routes for the delivery of PM cross-border

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Authors	Elena Doménech (ISCIII), Ángela Ponce Polo (ISCIII)		
Contributors	Juan Arenas (ELIXIR Hub)		
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1. Executive Summary

The question of the sustainability of 1+MG infrastructure goes well beyond funding, comprising several dimensions such as scientific excellence, socio-economic impact or innovation. All these questions should be addressed over the entire life cycle - from initial planning up to decommission.

In this deliverable, we compile different aspects that need to be taken into account for the future Genome Data Infrastructure (GDI) sustainability, resulting from the 1+MG initiative.

- Infrastructure needs
- Training needs
- Alignments with other initiatives and the EHDS
- Governance
- Investment needs
- Funding models
- Potential funding routes
- Socio-economic impact

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2. Contribution towards project objectives

With this deliverable, the project has reached or the deliverable has contributed to the following objectives/key results:

	Key Result No and description	Contributed
Objective 1 Engage local, regional, national and European stakeholders to define the requirements for cross-border access to genomics and personalised medicine data	**1.** B1MG assembles key local, national, European and global actors in the field of Personalised Medicine within a B1MG Stakeholder Coordination Group (WP1) by M6.	Yes
	2. B1MG drives broad engagement around European access to personalised medicine data via the B1MG Stakeholder Coordination Portal (WP1) following the B1MG Communication Strategy (WP6) by M12.	No
	3. B1MG establishes awareness and dialogue with a broad set of societal actors via a continuously monitored and refined communications strategy (WP1, WP6) by M12, M18, M24 & M30.	No
	4. The open B1MG Summit (M18) engages and ensures that the views of all relevant stakeholders are captured in B1MG requirements and guidelines (WP1, WP6).	No
Objective 2 Translate requirements for data quality, standards, technical infrastructure, and ELSI into technical specifications and implementation guidelines that captures European best practice	**Legal & Ethical Key Results**	
	1. Establish relevant best practice in ethics of cross-border access to genome and phenotypic data (WP2) by M36	No
	2. Analysis of legal framework and development of common minimum standard (WP2) by M36.	No
	3. Cross-border Data Access and Use Governance Toolkit Framework (WP2) by M36.	No
	Technical Key Results	
	4. Quality metrics for sequencing (WP3) by M12.	No
	5. Best practices for Next Generation Sequencing (WP3) by M24.	No
	6. Phenotypic and clinical metadata framework (WP3) by M12, M24 & M36.	No
	7. Best practices in sharing and linking phenotypic and genetic data (WP3) by M12 & M24.	No
	8. Data analysis challenge (WP3) by M36.	No
	Infrastructure Key Results	

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	9. Secure cross-border data access roadmap (WP4) by M12 & M36.	No
	10. Secure cross-border data access demonstrator (WP4) by M24.	No
Objective 3 Drive adoption and support long-term operation by organisations at local, regional, national and European level by providing guidance on phased development (via the B1MG maturity level model), and a methodology for economic evaluation	**1.** The B1MG maturity level model (WP5) by M24.	No
	2. Roadmap and guidance tools for countries for effective implementation of Personalised Medicine (WP5) by M36.	No
	3. Economic evaluation models for Personalised Medicine and case studies (WP5) by M30.	Yes
	4. Guidance principles for national mirror groups and cross-border Personalised Medicine governance (WP6) by M30.	No
	5. Long-term sustainability design and funding routes for cross-border Personalised Medicine delivery (WP6) by M34.	Yes

3. Methods and description of work accomplished

In this deliverable, we structure the information in sections that tackle the different aspects that may influence the sustainability of the 1+MG initiative and the European Genomic Data Infrastructure (GDI). To determine the content of these sections, we followed the following methodology:

We identified some relevant documents related to long-term sustainability of research infrastructure that are listed here below:

- ESFRI Scripta Volume II. Long-Term Sustainability of Research Infrastructures. European Strategy Forum on Research Infrastructures.[1] Long-Term Sustainability Working Group
- Sustainable European Research Infrastructures – a call for action. EC Staff Working Document[2]

We analysed the different aspects discussed in the documents to design and structure the content of this deliverable. In Table 1, we included the index of each of these documents and the corresponding sections in the deliverable:

[1] https://www.esfri.eu/sites/default/files/u4/ESFRI_SCRIPTA_VOL2_web.pdf

[2] https://op.europa.eu/en/publication-detail/-/publication/16ab984e-b543-11e7-837e-01aa75ed71a1/language-en

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Table 1. Mapping document analysed with deliverable sections

ESFRI Scripta Volume II.	EC staff working document	D6.10
Establish and maintain excellence	Ensuring scientific excellence	Infrastructure needs
Ensuring the right people are at the right place at the right time	Attracting and training the managers, operators and users of tomorrow	Training needs
Fully exploit the potential of RIs as innovation hubs	Unlocking the innovation potential of RI	-
Demonstrating the economic and wider benefit to society of RIs	Measuring socio-economic Impact of RI	Socio-economic impact
Harmonise and integrate the operation of RIs and e-Is	Exploiting better the data generated by the RI	Alignment with other initiatives and the EHDS
Effective RI governance, long-term funding and effective management	Establishing adequate framework conditions for effective governance and sustainable long-term funding for RI at every stage in their lifecycle	Governance Investment Funding models
Coordination at National and European levels	Structuring the International outreach of RI	Alignment with other initiatives and the EHDS

Moreover, we consider the recommendation 2 from the second B1MG review meeting to finally adjust the content of the deliverable. The Recommendation states the following:

B1MG should develop a clear sustainability plan by taking into consideration the economic, institutional, technological, governance and social/societal dimensions. All of them and the relation between them need to be considered. This plan should be used as a building brick for the GDI project, which is at the starting phase.

We reviewed other deliverables elaborated in other B1MG WPs to put together this information and have a complete overview of the current information regarding long-term sustainability of the infrastructure. The following deliverables were considered:

- [3]D2.4. Report on data access and governance framework
- [4]D4.1. Secure cross-border data access roadmap
- [5]D5.1. B1MG maturity level model and country-specific alignment within the model.
- [6]D5.2. Roadmap and guidance tool for countries.
- [7]D6.7. Guiding principles and best practices examples for mirror groups
- [8]D6.8 Policy briefs- 1v0

[3] https://zenodo.org/records/8411102
[4] https://zenodo.org/records/6139231
[5] https://zenodo.org/records/8383706
[6] https://zenodo.org/records/8403567
[7] https://zenodo.org/records/7565880
[8] https://zenodo.org/records/5727650

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Moreover, the content of this deliverable was elaborated by consulting some relevant bibliography (see section 9) and as a result of internal discussions.

4. Results and discussion

4.1. Infrastructure needs

The European 1+Million Genomes initiative (1+MG) aims to deploy a federated infrastructure providing access to genomic and phenotypic data in line with FAIR (Findable, Accessible, Interoperable, Reusable) principles. Its ambition is to enable secure access to high-quality genomics and the corresponding clinical data across Europe for better research, personalised healthcare and health policy making. This would imply the establishment of a federated, sustainable and secure infrastructure based on open community standards – the European Genomic Data Infrastructure (GDI).

The GDI will be structured as a federated network that connects genomic data resources through the supporting interoperable technical infrastructure within Member Countries, each country will establish a 1+MG Node (previously called National Contact Point or National Mirror Groups) to connect to the 1+MG initiative and support the national implementation. This federated approach ensures that authority, responsibility, and resources are primarily based within the Member Countries, and that Member Countries have a certain flexibility over how to implement the initiative at the national level according to their own characteristics. Data governance would be defined and agreed by the countries taking part in the establishment of the legal entity that will take over the 1+MG activities in due course.

We should distinguish the following stakeholders of the GDI:

- *1+MG Data providers*: The institutions who collected relevant genomic and or health data in a primary context of their own.
- *1+MG Data Requester/User*: The individuals and/or institutions seeking access to data (Data Requester),or granted access to data for a specific research project (Data User).
- *1+MG (Federated) IT Infrastructure:* Consisting of secure platforms in / for each Member Country where data are physically submitted, pre-processed, stored, and made discoverable and accessible.The IT Infrastructure must comply with technical interoperability requirements that are defined in 1+MG based on the work of WG5 to allow operations across the entire 1+MG network, where required.
- *1+MG Node (previously National Coordination Point):* A national node within Member Countries responsible for providing information on national rules for data inclusion, coordinating publication of a data catalogue, as well as coordinating search/access requests, and translating/publishing access/use information for a national audience or "lead" Data Provider. The 1+MG Node will be also responsible to support the national deployment of the data infrastructure as one key aspect of the 1+MG initiative

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- *Member Countries:* Countries that participate in the 1+MG legal entity and are subject to the 1+MG legal and/or governance frameworks. Ensure appropriate national legislation, governance, infrastructure and sustainability is in place and strive to harmonise these across countries.

Overall, this data infrastructure will provide five main functionalities:

- *Data discovery* provides the public visibility to the combined 1+MG dataset by making selected descriptive metadata searchable. Data discovery service will collect summary level (but not personal) descriptions and subject-level data of all data available from the countries. It will link directly to Data Access Management where users can apply for data access.
- *Access management tools*. Sensitive data needs specialised services to manage data in an ELSI compliant way. These include e.g. central access portal, central access review process, single collaboration/data use agreement. These tools support user applications for data use and the decisions from the data controllers, i.e. data access authorisations within the legal framework, as well as APIs and standards to communicate access rights to downstream infrastructure services. Together, these tools and processes facilitate and monitor and log the secure access for users on a chosen Data Processing service platform.
- *Data processing*. Local, high-performance and cloud computing must fulfil appropriate security standards to provide processing capacities for human data coordinated in 1+MG. Distinct processing events happen on the infrastructure: Localisation of the data and code to the appropriate platform (local or distributed) and data analysis by the individual data user who has acquired the access rights for the intended data use.
- *Data reception*. Uniform processes (such as quality control and standardisation) to receive or access (API) both data and metadata in a consistent way enabling infrastructure to adhere to global standards and principles (e.g. GA4GH, FAIR) for genotypic and phenotypic data. Data reception means logically describing datasets to an extent that they can become actionable on the 1+MG infrastructure even if they are stored nationally or locally.
- *Storage and interfaces*. Organisations store data and offer interfaces (APIs) following international standards that form the technically interoperable infrastructure backbone. Service building is assumed to leverage national and European investments in e-infrastructure capacities. Storage & interfaces need to provide techniques ensuring data privacy and confidentiality. In addition, some considerations should be taken into account about back-ups, dataset versioning, data archiving for research projects, etc.

The five service architecture functionalities (Data Discovery, Access Management, Data Processing,Data Reception and Storage and Interfaces) are required to make the data FAIR. To support these functionalities the data and metadata representation must be harmonised by

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following the recommendations of 1+MG and B1MG, machine-actionable where possible, and meet minimal quality standards defined by the 1+MG initiative.

Managing the whole genome sequences of 1+million individuals requires a data infrastructure capable of storing PBs for data with suitable backup (for example distributed replication) connected to high-performance computing, as well as access management and data discovery services.

4.1.1 Training and capacities needs for the data infrastructure

The development, deployment and operations of the 1+MG Data infrastructure at the European level would require building skill and capacity in a number of areas.

- ELSI expertise: To ensure the constant flow of data for secondary use each 1+MG Node would be required to build the ELSI expertise to ensure data subject rights are protected fulfilling applicable regulations including the data governance processes and principles that would be established to operate under the 1+MG legal entity once established.
- Data management/stewardship: Ensuring a constant flow of high-quality genomic and phenotypic data into the infrastructure would require the deployment of data management capacity to ensure the conform to the 1+MG minimal metadata model, adhere to the required quality and it is annotated not only according to the semantic model to describe the data but also incorporate all operational metadata required to facilitate discovery and provide appropriate access in line with the appropriate use.
- Technical expertise: The development, maintenance and operation of the 1+MG technical infrastructure would require a combination of technical skills in each node so they can support the roll out of the infrastructure at the national level.
- Users Training: Uses of the 1+MG infrastructure would require training material and support when registering into the infrastructure, applying for access, discovery data (catalogue or federated queries), make their analytics / AI model ready for the infrastructure, run their model and access the results.
- Data subjects: Would require an easy access to the adequate level of information (in their one language) to understand how their data is being used, where it is used, and which is the impact of their contributions and, depending on the final data governance, opt in or out of their participation in the studies.

4.1.2 Training and capacities needs in health care system

Highlighted by the work done in WP5 around the deployment of genomics medicine, the introduction of digital technologies in healthcare systems presents many complex issues in relation to patients' rights, access to technologies, risk transfer in decision-making, secondary

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uses and, among others. In order to address this challenge a number of priorities should be established, such as:

- Developing the infrastructure and the digital health services oriented towards individuals, organisations and the processes that make up the health protection system, with a focus on equity.
- Training, involving and empowering healthcare professionals in the use of novel digital technologies and facilitating their relationship with health services by promoting their participation at all levels and encouraging their joint responsibility.
- Maximising the value of processes for better performance and efficiency of the public health system, supporting the work of professionals and facilitating communication between them in a way that ensures continuity of care and strengthens the governance of organisations.
- Generalisation of the interoperability of health information by adopting data management and governance policies taking EDHS rules into account.
- Boosting data analytics related to health, the determining factors and the health system.

Several countries have already developed Digital Health Strategies where these priorities are considered, such as Spain. Together with Digital Health Strategies, countries have also developed the National Health Genomics Plan and National 1+MG Roadmap, which is a massive step towards delivering personalised medicine to all citizens in Europe.

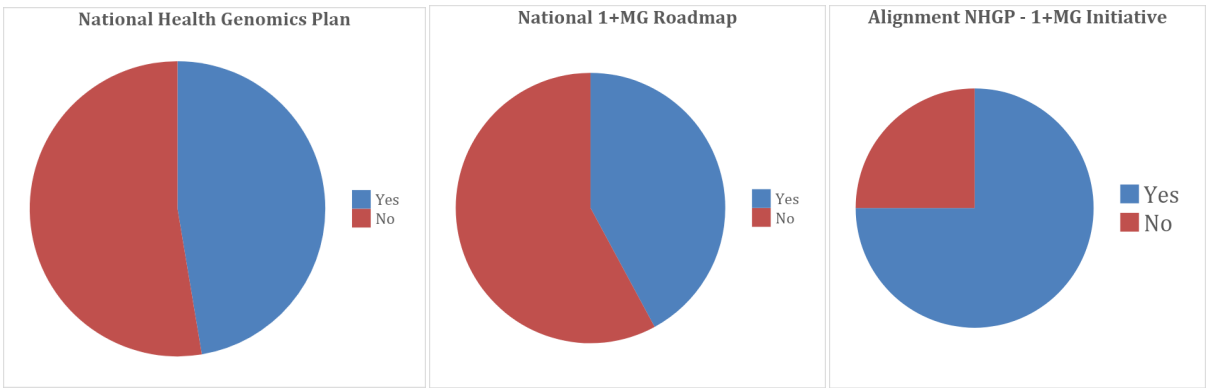

Figure 1. Results from the B1MG-D6.7. Guiding principles and best practices examples for mirror groups survey.

However, according to B1MG-Policy Brief: Genomics in Healthcare Key issues for implementation, some challenges should be still to overcome in the implementation of genomics into healthcare, including:

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- Patient and citizen engagement (examples of actions to take)
    - Monitor patient trust and willingness to give samples and consent for the use of genomic based diagnosis and treatments.
    - Involve patient groups in all decisions and steps of implementing the genomic strategy since the outset of the programme, including discussion of the legal framework.
- Ensuring a robust , safe and trusted infrastructure:
    - Create an infrastructure with centralised governance and a robust ethical and legal framework for secure and transparent collection, analysis and use of data.
    - Ensure solid investment in secure digital technologies and services.
    - Seek inter-ministerial collaboration and inclusion of all stakeholders for implementing the strategy, gaining investment in public-private partnerships, and earning solid and steady political support.
    - Implement a standard genomic and health data management plan to facilitate sharing information for clinical and research at regional, national and international levels.
- Training and capacity building:
    - A competency framework with different levels for individuals and organisations to evaluate the need for increased knowledge/skillsInvest in developing professionals, namely clinical geneticists and genetic counsellors, and new professions, such as medical informaticians
    - Define the roles of these and other professionals, such as general practitioners that specialise in clinical genetics and provide counsel related to genomic information.

In the B1MG project, a maturity level model was developed to assess the readiness of each country to implement genomics in their respective healthcare system. The maturity level comprises different dimensions:

1. Governance and strategy
2. Investment and economic model
3. Ethics, legislation and policy
4. Public awareness and acceptance
5. Workforce skills and organisation
6. Clinical organisation, infrastructure and tools
7. Clinical genomics guidelines and infrastructure
8. Data management, standards and infrastructure

Analysis of the pilot in 8 countries led to the following observations on the topic of training needs:

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1. Training in genomics is available in medical curricula in most of these countries, but in some is still under implementation. Only one country mentioned not having genomic training in medical curricula.
2. Training in genomics for nurses is not available in most countries, but needs and gaps are identified and training options are under development.
3. There are wider asymmetries across the pilot countries regarding training in genomics for pharmacists, with over half the countries already having training available, but the remaining countries with no training or training under development.
4. The largest majority of countries (6 out of the 8) have training programs for genetic counsellors.
5. The majority of countries do not have any programs to raise awareness of policy makers and healthcare managers regarding genomic medicine, or have programs under development; only 2 countries reported having programs under implementation.
6. There is a wide asymmetry across countries in terms of life-long or continuing education programs in genomic medicine for different healthcare professionals. For the majority of countries training was under implementation or already implemented, but several countries did not have any programmes or were assessing needs and gaps.

In conclusion, basic genomic medicine training is not necessarily available for different health professionals and across European countries. It is stronger for medical doctors and weaker for nurses, but there are genetic counselling training programs in most countries. Not much is available to improve the literacy in genomic medicine for decision makers. Finally, the observed asymmetries across countries can be improved through european-wide sharing of existing education programs.

4.2. Alignments with other initiatives and the EHDS

There are numerous projects and initiatives in Europe in the field of biomedical and health data processing for research, personalised healthcare and precision public health purposes that should be analysed to identify possible overlaps, gaps and, above all, to promote synergies.

TEHDAS and TEHDAS2 are especially relevant for the 1+MG because of their secondary use of data. TEHDAS and TEHDAS2 are joint actions Towards the European Health Data Space that helps EU member states and the European Commission to develop and promote concepts for the secondary use of health data to benefit public health and health research and innovation in Europe. Although TEHDAS is already finished, it elaborated a number of documents and recommendations to be considered within the 1+MG framework and will have continuity with TEHDAS2

In the scheme here below, we propose a scenario where 1+MG could play the role of TEHDAS in an imaginative “Genomic Data Space” that should be integrated, via federated clinical-genomic

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database into the EHDS. In addition, it displayed some policy bodies together with possible funding sources and the example of Spain organisation to contribute through the IMPACT project to the 1+MG database.

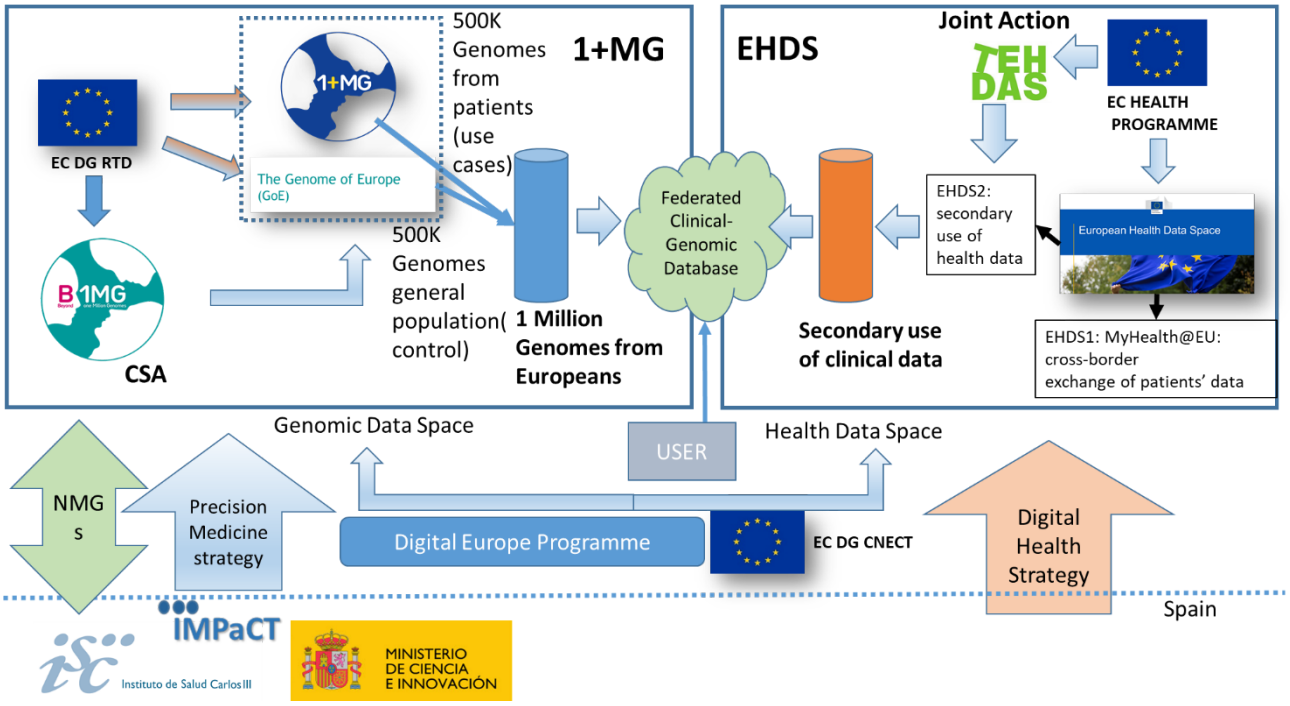

Figure 2. Scheme about the interconnection between 1+MG, TEHDAS and EHDS

Another important project to follow up is HealthData@EU, a two-year project co-financed by the EU4Health programme. It will build a pilot version of the European Health Data Space (EHDS) infrastructure for the secondary use of health data "HealthData@EU". The project aims to connect data platforms in a network infrastructure and develop services supporting the user journey for research projects using health data from various EU Member States.

4.3. Governance

The European Digital Infrastructure Consortium seems to be the legal entity most appropriate to implement the 1+MG initiative at this point according to *D2.4.Report on data access and governance framework*. A deeper analysis of this legal entity model should be performed in the GDI project to identify pros and cons before making the final decision.

Hereafter, we will advance some of the aspects that should be taken into consideration regarding the EDIC as a legal entity for 1+MG :

Purpose. EDIC is a legal entity devoted to implement "multi-country projects", that means large-scale projects facilitating the achievement of the digital targets.
Statutory seat. EDIC shall have a statutory seat, which shall be located on the territory of a Member State that is a member providing a financial or non-financial contribution.

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Membership. At least three Member States. Only Member States that provide a financial or non-financial contribution shall be eligible to become members of the EDIC. Members that do not contribute may join as observers.

- Third countries will be allowed if they are associated to a directly managed Union programme supporting the digital transformation and their participation is needed to accomplish the EDIC objectives. International organisations of European interest, and public or private entities, could also be members as specified in the Statutes of the EDIC.
- Where appropriate, a Member State participating in a multi-country project may delegate the implementation of its part of that project to a region, in line with its national roadmap.
- Voting rights. Only for those countries that provide any contribution (financial or non-financial). Member States shall hold jointly the majority of the voting rights in the assembly of members, regardless of the amount of contributions from entities other than Member States. The Commission shall participate in the deliberations of the assembly of members, without itself having voting rights.
- Governance. An EDIC shall have at least the following two bodies: 1) an assembly of members and of the Commission (without voting rights), 2) a director, appointed by the assembly of members, as the executive body and legal representative of the EDIC.
- Liability. The financial liability of the members for the debts of the EDIC shall be limited to their respective contributions provided to the EDIC.
- Applicable law and jurisdiction. a) By Union law, in particular by this Decision; b) by the law of the Member State where the EDIC has its statutory seat; c) by the Statutes and their implementing rules.
- Reporting by and control. An EDIC shall produce an annual activity report, containing a technical description of its activities, and a financial report.
- Setting up an EDIC. Members shall submit a written application to the Commission, containing the following: 1) a request to the Commission to set up the EDIC; 2) the proposed Statutes of the EDIC; 3) a technical description of the multi-country project to be implemented by the EDIC; 4) a declaration by the host Member State whether it recognises the EDIC as an international body. The Commission shall assess the application and adopt by means of implementing acts either of the following: a) a decision setting up the EDIC, b) a decision rejecting the application, which implies for Members States to form a consortium by way of an agreement.
- Financially, the EDIC legal entity is eligible for public funding programmes as Horizon Europe and for VAT Exemption tax. Additionally, it opens the door to implement some fees for the country members.

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4.4. Investment needs

Calculating the costs of a digital research infrastructure to provide genome sequence data and associated clinical information to researchers and clinicians Europe-wide can be a complex process and will depend on several factors, including:

Infrastructure requirements: The cost of the digital research infrastructure will depend on the infrastructure requirements such as the number of servers, storage capacity, network bandwidth, and other computing resources needed to store, process, and distribute genomic and clinical data.
Data volume: The amount of data that needs to be stored and processed will have a significant impact on the infrastructure's costs. Genome sequences are typically large, and the cost of storing and processing large datasets can be substantial.
Scalability: The digital research infrastructure should be ideally scalable to handle increasing amounts of data as more researchers access the system. It is also necessary to include scalability costs when calculating the infrastructure costs. However, more discussion about whether or not scalability is possible in the 1+MG infrastructure is needed.
Staffing: The cost of staffing the infrastructure team, including system administrators, software developers, and bioinformatics experts, should also be considered.
Licences: The cost of licences for the necessary software and tools required for the infrastructure should be included in the cost calculation.
Maintenance and support: The cost of maintenance and support for the digital research infrastructure should be included in the calculation. This includes software updates, security patches, and hardware maintenance.

The choice of software, licences and IT service providers will likewise influence the investment and longer-term financial needs, in particular where systems are evolving. The cost will further depend on the data governance that determines responsibilities at national and central level. Responsibility on the local and central level is further interlinked with technical and organisational functions.

It is also important to note that the costs of a digital research infrastructure can vary significantly based on its specific requirements. Thus, the final design of GDI will have a strong influence on the running cost and therefore on its sustainability.

To estimate the costs, we can use the following steps:

1. Estimate the amount of data that needs to be stored and processed.
2. Determine the infrastructure requirements based on the data volume and expected usage.
3. Determine the staffing required for the infrastructure according to their roles.
4. Estimate the cost of software licences, maintenance, and support.
5. Calculate the total cost of the infrastructure over a specified period, such as a year.

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6. Adjust the cost calculation based on factors such as inflation, changes in data volume, data access requests, user interactions or changes in infrastructure requirements.

For the GDI, it is envisioned a model where we have a division for the data access management procedures and costs:

Local / national efforts should be covered nationally
Central costs will be covered centrally

The local / national efforts could be the *in-kind* contribution of the country to make all the infrastructure and procedural workflows available. As Data Providers may be located within existing facilities, cost items attributable to them should include shares of time machine,personnel costs, among others directly related to the use of the infrastructure for the GDI needs. .

Regarding central costs, we will analyse different funding models in the GDI project although we propose some of them in this deliverable (see section 5.6).

Cost estimation

The StR-ESFRI study[9] on Guidelines on cost estimation of Research Infrastructures, contains the methodology proposed to determine the central costs of a research infrastructure:

1st) Define the unit of analysis.

GDI is envisioned as a distributed infrastructure where each Member country will have some flexibility in order to establish the 1+MG (Federated) IT Infrastructure as they could include different 1+MG Data Providers s. Each of these Data Providers will have different costs, and we should be able to estimate these costs. The unit of analysis will then be the sum of the costs of each component, disregarding its geographical location. Considering this distributed organisation, we could distinguish:

The costs of central hub for service provision;
The costs of central hub for coordination;
The cost of national nodes for the coordination of local entities;
The costs of national/local nodes for research activities and/or service provision.

In order to estimate and also monitor the infrastructure costs, it is important to have the commitment from the Data Providers to share and facilitate financial information and establish a procedure to define which information will be analysed and monitored. This exercise to gather

[9] https://www.esfri.eu/sites/default/files/StR-ESFRI2_STUDY_RIs_COST_ESTIMATION.pdf

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all the data would be too time-consuming when the number of sub-entities is too high. At the initial stages, an approximation could be made at a more aggregate level.

2nd) Adopt a long-time horizon.

Cost estimates must take into account the entire lifecycle of the infrastructure, which means considering the costs spanning the entire period of time during which the facility remains useful. Total costs include both investment and operating costs.

In the case, the Member country decides that the Data Provider infrastructure needs to be built from scratch, the standard pattern shows a relatively large investment peak during design, preparation and construction (see figure 3). However, GDI should rely on existing infrastructures, whose set-up phase includes only minor investment costs as compared to the operational costs .

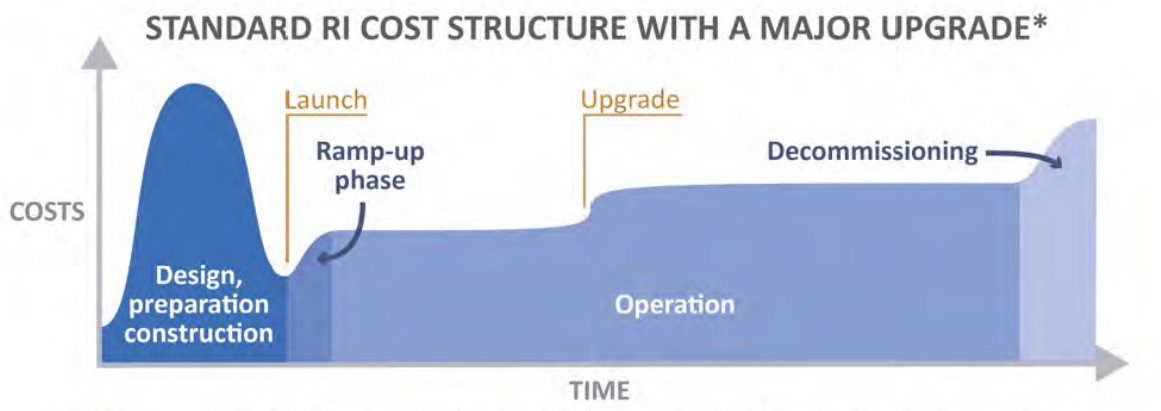

Figure 3. Standard RI cost structure with a major upgrade

There are Member States, which have developed data sharing infrastructures that could act as Data providers for the GDI. Thus, the organisational aspects of the infrastructure should be analysed to facilitate the estimation of the initial investment costs for the implementation of the GDI.

3rd) Fix the start date.

The time horizon starts the year when the first resources are deployed (cash or in-kind) for the design and preparation phase of the RI. Re-use of components of existing facilities are 'sunk' costs and should not be included.

4th) Fix the base year.

The basal year is the point-in-time when the cost estimation is made and it does not necessarily coincide with the start date. Past and future costs should be intended with respect to the basal year.

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5th) Costs should be expressed in real terms.

Prices must be constant at the base year: future costs must be forecasted according to realistic assumptions and should be net of inflation while past costs, usually reported in financial statements, must be converted into base year value by applying the inflation index.

6th) Only cash outflows are reported.

The cost accounting must follow a cash flow method. Depreciation, reserves and other accounting items that are usually reported in balance sheets must not be included. Sources of funding can be used to identify cost items but shall not be mixed or added to them.

7th) *In-kind* contributions must be included.

An *in-kind* contribution is a contribution of a good or a service other than money. This aspect can be related to the use of donated scientific equipment or the exploitation of machine time or personnel costs. Although such arrangements correspond to the use of real resources, they do not appear in the budgetary cost as a cash flow (but can appear in the budget of the donating/participating partner institution). They are however relevant costs and, as a general rule, should be considered at their current market price.

8th) Cost must be expressed in Euro.

9th) Costs must distinguish between investment costs and operating costs.

Costs must distinguish between investment costs and operating costs. Hereafter, we will enumerate the costs defined as “investment costs” or “operating costs”.

Although it will vary according to Member countries’ decisions about their 1+MG (Federated) IT Infrastructure, investment costs would include

Design and preparation. Design and preparation costs are all the in-kind and cash expenditures needed for the conceptual design and feasibility study of the infrastructure. They also include the costs for the preparatory phase , including possible interim-phase after the preparatory project. The main items included in this cost category are scientific, technical and managerial personnel costs; networking activities; joint-research activities and trans-national cooperation. In-kind contributions in this phase can be mainly in the form of *in-kind* contributions of personnel. These costs are covered by the contribution from the EC and the Member States involved (co-funding) through the B1MG and GDI projects.

Construction and start-up relate to the set up and launch from a physical, institutional, legal, organisational and managerial point of view of the infrastructure:

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2.1. Physical (e.g., land acquisition, installations, constructions) and non-physical (e.g., IPRs, cloud, other information technologies) assets, usually the major component of initial investment costs;

As we said, 1+MG EFGI could rely on existing infrastructures and these costs could include only minor investment costs as compared to the operational cost. These investments could be included as in-kind contributions.

2.2. Personnel. They can include scientific, technical, administrative and managerial personnel costs. When the personnel may be involved in different activities also not related to the GDI in existing infrastructures , it is important to include only the share of his/her work-time actually dedicated to the as documented in timesheets or similar internal records. *In-kind* contributions are also usually in this type of cost.

2.3. Consumables, utilities and other costs. This includes all the costs incurred during the initial phase to set-up the facility which are not included in the previous categories. They can include the use of energy, water or waste disposal, travel and other costs for networking and joint research activities..

2.4 Start-up costs (e.g. training, licences, etc.). They include all costs related to the launch of operations, including training costs and acquisition of licences and patents.

These costs will depend on the involvement or not of the existing infrastructures for the deployment of 1+MG.

There are other costs related to the operational status of the infrastructure to upgrade the infrastructure, which are not relevant at this stage but should be considered for the long-term sustainability of the infrastructure:

- Replacement costs correspond to the capital expenditure required to replace those assets whose economic lifetime is shorter than the reference period.
- Major upgrades. Extraordinary maintenance and major upgrades are considered as investments cost, which occur during the operational phase and are related to the modernization and expansion of the facility.
- Decommissioning and end-of-life costs. End-of-life costs relate to any decommissioning costs and/or environmental mitigation costs that may be necessary at the end of the time horizon to dismantle the whole or individual components of the fixed assets.
- Residual value. The residual value reflects the capacity of the remaining service potential of fixed assets whose economic life is not yet completely

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exhausted. It must be included for the end-year and with a negative sign, since it is an inflow. It will be zero or negligible if a time horizon equal to the economic lifetime of the asset has been selected or if decommission costs are particularly high. It is the only inflow item of the total investment costs.

Operating costs should be distinguished between fixed (for a given capacity, they do not vary with the volume of goods/service provided) and variable (they depend on the volume).

It should be noted that operating costs tend to be relatively constant when the infrastructure is running at full capacity, but in the start-up and launch phase, before arriving at full capacity, there is a ramp up phase, which can last some years. Measures such as the net present value provide much more insights, compared to the annual average, for the aims of cost estimation.

Typical operating costs include; rent of buildings or sheds, rental of machinery; personnel; ordinary maintenance and repair of assets; utilities (consumption of raw materials, fuel, energy supply) and consumables; users support, services purchased from third parties. Other operating costs may include: environmental protection measures, general management, and administration and quality control costs, royalties paid for the use of patented products or processes, promotional campaigns and other outreach expenditures.

10th) Total costs must be calculated at present value.

Future costs must be discounted while past costs must be capitalised (in addition to inflated, as explained at point 5) with an appropriate discount factor.

This is the first approach about the methodology and possible cost elements for the creation and deployment of the GDI. A more detailed analysis needs to be developed in the GDI project.

4.5. Funding models

The document OECD Global Science Forum - Business models for sustainable research data repositories provides a typology of revenue sources:

- **Structural funding** (i.e. central funding or contract from a research or infrastructure funder that is in the form of a longer-term, multi-year contract). We use the term “structural” to underline the difference between this and project funding. Although the funding must be regularly reviewed, it is a form of funding that is substantively different to project funding.

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If there is an explicitly defined required contribution from each partner, it might be based on different modes of calculation, for example:

- Fixed, identical contribution for all the partners.
- Contributions based on GDP or GDP per capita, or some other relevant indicator.
- Contributions based on an algorithm agreed between the partners.

Contributions could be made in cash or *in kind*. The distinction can be a critical one, and needs to be the subject of dedicated discussions during the establishment phase. Usually, *in-kind* contributions (such as personnel, equipment, office space, utilities, software, hosting of meetings, editing and publishing) are easier to arrange.

- **Host institution funding and support** (i.e. direct or indirect support from a host institution). Some research infrastructures are hosted by a research performing institution, e.g. a university, and receive direct funding or indirect (but costed) support from their host.

- **Member fees** could be an option for those countries that would like to be members of the EDIC but without any *in-kind* contribution. The majority of the ERICs use this model to ensure their sustainability.

- **Access charges** (i.e. charging for access to standard data or to value-added services and facilities). This covers charges of various sorts (e.g. contract or per-access charges) and can be levied either for standard data or value-added services. In all cases, the cost is borne by the entity that wishes to access and use the data.

  This solution could be an option if we open the access of the data infrastructure to the industry or non-country members. This pricing approach should be discussed taken the access request conditions (resources to access) into account.

- **Contract services or project funding** (i.e. charges for contract services to other parties or for research contracts). This covers short-term contracts and projects for various activities not covered above (i.e. these are not contracts to deposit or access data, but cover other services that may be provided). Similarly, this category of funding is distinct from structural funding because, although it may come from a research or infrastructure funder, it is for specific, time- and objective-limited projects, rather than for ongoing services or infrastructure.

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Contract for services could be an additional option for the participation of the industry or non-country members if they frequently ask for services to the infrastructure.

Models combining various revenue sources

Combining revenue sources into a sustainable model is an important element of developing a sustainable research infrastructure. Diversification of revenue sources is attractive, as it has no single point of failure and the financial risks are spread. It offers flexibility to experiment with new services and markets and can stimulate innovation, which might not be supported from core funding sources.

The flipside is likely to be a relatively higher administrative overhead. With different funders, with possibly diverse and shifting interests, attention could be drawn away from the core mission of the data repository or lead to mission creep or confusion. Moreover, making the business case to a range of funders with different stakeholder perspectives may prove difficult.

EXAMPLES

ELIXIR shows a mixed funding model with contributions coming from a number of mostly public sources. Collectively (and also separately), the ELIXIR Hub and Nodes compete for grant funding from the European Union. The ELIXIR Hub is funded through membership fees paid by Member countries, and much of this funding is then transferred back to Nodes to implement ELIXIR´s five-year Scientific Programme. ELIXIR Nodes, which run the services that users access, are typically funded through national-level investments that support the national coordination within the Node. The development and operation of services is usually funded through national grants, sometimes through dedicated infrastructure grants but, more frequently, through competitive research grants where service development is one component.

ELIXIR Nodes also receive support from international funders such as the US National Institute of Health (NIH) and foundations (e.g. the Wellcome Trust and Wallenberg Foundation). A small number of ELIXIR Nodes receive income from industry engagement, though the volume of this is modest compared to the public funding they receive. Finally, some ELIXIR Nodes also access EU Structural Funds to support national coordination and the purchasing of facilities.

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Figure 4. ELIXIR business model

As well as ELIXIR is funded through public investments, one of its core missions is to ensure that bioinformatics resources remain a "public good" that is as open and free to users as possible. An exception to the principle of free access that offer access to depletable resources includes some computing services in High Performance Computing (HPC); in this case, user fees are charged, based on the user's location and field (academic, industry).

TEHDAS´ preliminary study on funding sources and costs of secondary use of health data in the EU

Building a European data access and sharing system will have an impact on the national data collection and access mechanisms, leading to a need to develop national systems. It will raise questions of funding the costs to the governments of developing their national systems as well as joining the European data exchange. The cost sharing principles between the EU and Member States and funding through the EU and national budgets need to be thoroughly discussed.

The adoption of a common framework is essential, not only for gathering data and supporting funding decisions, but also to allow update and verification of the information. It can also be used by RI managers for more far reaching exercises such as assessing the socio-economic impact of the RIs (particularly with the use of cost-benefit analysis) or ensuring long-term financial sustainability and, ultimately, facilitating the dialogue with funding agencies.

In order to study sustainability elements of the EHDS, an analytical framework is needed. The TEHDAS user journey model and the catalogue of relevant services is completed with earlier and later stages in the economy of the secondary use of health data.

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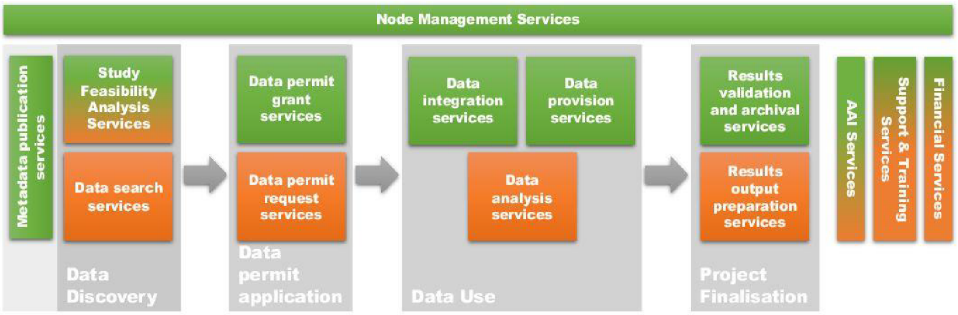

Figure 5. TEHDAS user journey

In the analytical framework, the first stage is data collection that is carried out for the primary purpose of the data use, which does not necessarily consider its secondary use. The second stage is the data access management as defined in the user journey. The last stage in the data economy is the actual analysis for research or other secondary purposes. In the framework, it is necessary to discuss possible sources for funding and various types of costs.

The data economy has many policy-related aspects beyond the operational costs of the EHDS. However, they will be relevant in the policy making process.

4.6. Potential funding routes

4.6.1. Funding Programmes

Digital Europe programme: is the central programme for digital in the Multiannual Financial Framework (Horizon Europe). It aims to accelerate economic recovery and drive the digital transformation of Europe.

The Digital Europe Programme will strengthen investments in a range of areas, including:

- supercomputing and data processing capacities;
- core artificial intelligence (AI) capacities such as a data spaces and libraries of AI algorithms;
- cybersecurity;
- digital skills, expanding the best use of digital capacity in EU's society and economy;
- support to the digitalisation of businesses and public administrations

The Digital Europe Programme is conceived to fill the gap between research and deployment of digital technologies. It will bring the results of research to the market for the benefit of Europe's citizens and businesses, in particular small and medium-sized enterprises SMEs).

Digital Europe Programme: Worth €7.6 billion in current prices.

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Horizon Europe: is a 7 year funding programme for research and innovation that will continue the work of Horizon 2020. It will fund vital research in health, resilience and the green and digital transitions.

Horizon Europe includes a dedicated budget for 'Digital, industry and space'. This budget will develop research and high-end innovation in enabling technologies, such as:

- artificial intelligence and robotics
- next generation Internet
- high performance computing
- big data
- key digital technologies
- 6G

It will also aid research into combining digital with other technologies. Overall, it is expected that around 35% of Horizon Europe will support work for the digital transition. The work of Horizon Europe will be complementary to that of the Digital Europe Programme.

Of particular importance are the Missions, which set out measures to achieve bold, inspirational and measurable goals within a set timeframe. There are 5 main mission areas as part of Horizon Europe (with a particular relevance in this scope the Cancer Mission).

Horizon Europe: €95.5 billion in current prices.

Connecting Europe Facility - Digital

The Connecting Europe Facility supports trans-European networks and infrastructures in the transport, telecommunications and energy sectors. It is investing in broadband networks, as a part of the EU's wider efforts to build infrastructure that can handle emerging and future processes and applications

Connecting Europe Facility – Digital: Worth €2.07 billion in current prices.

European Structural and Investment (ESI) Funds

The European Structural and Investment Funds (ESI Funds) provide substantial investments in Research and innovation. Also, for less research intensive regions of the EU, significant amounts of resources are available via ESI Funds. ESI Funds, are being used by some Member States to cover construction costs, but their expected impact is not always in line with the RI objectives nor the regional development objectives

In order to exploit this opportunity, it is important to reconcile the long-term competitive advantages resulting from RI with the short-to-mid-term socio economic advantages that qualify for the use of ESI Funds, by improving the cost-benefit assessment methods for RIs and enhancing their relevance for the national or regional economy.

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Another example is the ICT investments for over €20 billion from European Regional Development Fund (ERDF), focusing on digital cohesion across the EU.

EU4Health

EU4Health is a new programme intended to strengthen health security and prepare for future health crises. Approximately 10% of this programme will be of use for digital transformation of the health sector.

Partnerships

Figure 6. Partnerships in the Horizon Europe programme

Innovative Health Initiative (IHI)

This partnership intends to

- create an EU-wide health research and innovation ecosystem that facilitates translation of scientific knowledge into innovations
- foster the development of safe, effective, people-centred and cost-effective innovations that respond to strategic unmet public health needs currently insufficiently served by industry
- drive cross-sectoral health innovation for a globally competitive European health industry.

It will cover prevention, diagnostics, treatment and disease management.

Transforming Health Care Systems (THCS)

The partnership aims to contribute to the transition towards more sustainable, resilient, innovative and high-quality people-centred health and care systems.

It will pool a critical mass of European, national and regional scientific resources to more efficiently address similar challenges related to health and care systems transformation.

As a result, the context relevant evidence will meet the needs of national/regional health and care systems by facilitating the transfer and uptake of cost-effective technological, service, organisational and policy innovations.

Rare Diseases (EP RD)

The partnership will coordinate national, local and European research and innovation programmes, combining research funding and implementation of research supportive activities such as training, data access infrastructures, data standards etc.

The main goal is to improve the life of patients with rare diseases by developing diagnostics and treatments for rare diseases through multidisciplinary research and innovation programmes with all relevant stakeholders. This will increase impact and uptake of research results as well as increase the visibility of EU leadership in rare diseases research.

Personalised Medicine (EP PerMed)

The partnership aims to coordinate research in personalised medicine between the EU, EU countries and regions.

Aims:

- faster uptake of research and innovation results into clinical practice, secure Europe's position in state-of-the-art healthcare provision
- facilitate a shift from a 'one size fits all' approach towards taking into account individual differences and better utilising the accumulating data to manage health, disease and its predisposition
- sustainable health systems and independence in data intensive healthcare

EOSC Partnership

The partnership will enable a trusted, virtual, federated environment in Europe to store, share and re-use research data across borders and scientific disciplines. Besides, it will bring together institutional, national and European initiatives and engage all relevant stakeholders to co-design and deploy a European Research Data Commons where data are Findable, Accessible, Interoperable, Reusable (FAIR).

InvestEU

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The InvestEU Programme, whose budget stems partly from Next Generation EU, is able to provide crucial support to companies in the recovery phase. At the same time, and in line with its original goals, it ensures a strong focus of investors on the EU's medium- and long-term policy priorities such as the European Green Deal, the European Green Deal Investment Plan and the Strategy on shaping Europe's digital future.

InvestEU also supports activities of strategic importance to the EU, in particular in view of enhanced resilience and of strengthening strategic value chains.

Strategic Technologies for Europe Platform (STEP)

The Strategic Technologies for Europe Platform (STEP) is the European reply to the need to boost investments in critical technologies in Europe.

STEP seeks to reinforce, leverage and steer EU funds – existing and new – to investments in deep and digital, clean and biotechnologies in the EU, and in people who can implement those technologies into the economy.

The STEP Platform will improve access to finance for start-ups in the EU by pooling funding under existing programmes and mobilising untapped sources of private capital. This will support the new wave of deep tech innovation across the EU.

4.6.2. Other funding routes

The EU funding programmes only cover a fraction of the infrastructure overall activities for the integration and opening of national research infrastructure and the initial development of pan-European RI - through grants and loan guarantees. Therefore, this source is not enough to cover all the costs that a federated genomic infrastructure should face. In this section, we propose some other sources and measures that may contribute to the long-term sustainability of the infrastructure.

- **Encourage synchronisation of national roadmaps and their alignment with the European RI roadmap;**

Many infrastructures are extremely expensive with construction price tags that can go well beyond a 5 billion Euro and related operational costs that, on average, on a yearly basis, amount to around 10% of their construction value.

National Genome Data Strategy Decisions and emerging genomic data technologies should be included/considered to the national node. In this sense, each country should align their National Health Genomics Plan with the 1+MG initiative and may provide a stable financial scenario to ensure the maintenance and the upgrade of the infrastructure. Nonetheless, the investment decision on the national IT infrastructure will be considered at national level. If a country makes its own workflows costly, it should be themselves who pay for it.

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This decision could be challenging for the long-term sustainability of the European federated genomic infrastructure as it will imply differences in national budget cycles and of the validity and timing of updates of national roadmaps. To overcome this issue, countries should reflect on the identification of other additional funding instruments such as ESI Funds. Another solution proposed by ESFRI Forum is to see whether financial contributions to ESFRI projects, ERICs and EDICs could be supported on national budget lines similarly as for international treaty-based organisations. This could provide a sufficient stable investment environment.

- **Collaboration with the industry**

Acknowledging the role of industries in the scale-up and sustainability of these efforts, several ways need to be explored such as the role of companies as key stakeholders in realising cross-border genomic data sharing efforts, developing a practice of genomics-based personalised health in 1+MG associated countries and participating in funding public-private programmes, such as under the framework of IHI.

Another aspect to consider is what the likeliness of industry is towards co-investing in 1+MG data infrastructure services and sustainability and industry's long-term strategy for data sharing. The Australian Translational Genome Center is an example of a public-private nature of national genomics efforts, which help build better relationships between stakeholders working towards the same goal.

Additionally, the industry would have valuable technical expertise useful in the context of 1+MG: automation, cloud servers, but also resources for cybersecurity.

- **Improve the data infrastructure' costs coverage;**

Improving the coverage of costs implies a higher visibility for their services to the research communities. Turning operational costs eligible in research grants, at a national and European level. For instance, in the form of a fixed percentage that would be added to the user costs allowing for the infrastructure to undertake maintenance could be beneficial for the sustainability.

- **To establish a business model**

The definition of business models is a critical tool to foresee how a company will make money or in the case of non-profit entities, how they can ensure their sustainability in the long-term. The development of a credible business plan during the preparatory phase of a research infrastructure is recognized as Imperative to improve the bankability of infrastructures.

The Business Model Canvas is a strategic management template used for developing new business models and documenting existing ones. It offers a visual chart with elements describing the value proposition, infrastructure, customers, and finances, assisting businesses to align their activities by illustrating potential trade-offs.

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The traditional canvas model has nine boxes: customer segments, value propositions, channels, customer relationships, revenue streams, key resources, key activities, key partnerships, and cost structure. At this point, it is premature to complete a canvas template for the future European federated data genomic infrastructure but it is important to have already in mind these aspects in order to continue discuss and analysed their influence in the future sustainability of the infrastructure:

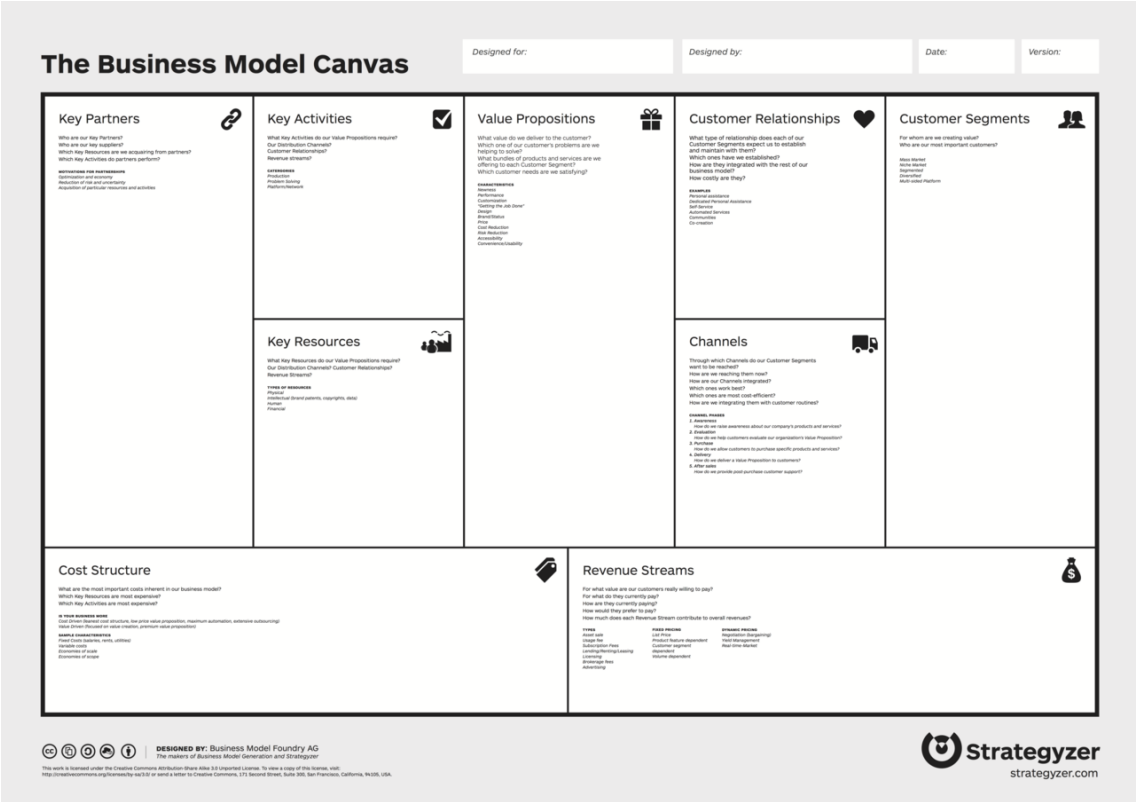

Figure 7. Business model Canvas

In this deliverable, we slightly initiate some revenue streams (see section 4.6) and how to calculate the cost structure for the European federated data infrastructure (see section 4.5.).

4.7. Socio-economic impact

Research infrastructures have a direct impact on society primarily in function of the knowledge generated through the services they offer. complementary, a set of direct economic impacts tied to activities such as the employment of the workforce during their construction and implementation phase or the creation of new jobs and services for their operation and maintenance.

In addition, the EFGI will be the first infrastructure where the research and health applications hold hands. This would contribute to advanced research, disease prevention and personalised health and care in key areas including rare, infectious and complex diseases.

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Other socio-economic impact pursue by the 1+MG initiative are the following:

- The use of genomic medicine will help health systems to meet the challenges they face and become more sustainable.
- Ensuring the competitiveness of the Union in the global race to advance personalised medicine, and that its citizens benefit from the latest innovation in this field.
- Scaling up digital health and implementing data-driven digital solutions.
- Leading to more cost effective use of health care resources in the Union and new approaches to care delivery which better address the needs of individual patients.
- To enable targeted research and innovation as well as efficient translation of that research into clinical settings and public health work, which can lead to more effective therapies for individual patients and improved preventive measures.
- To advance the understanding of genetic associations that cause or predispose diseases.

In addition to these aims including in the 1+MG Declaration, it may be a good idea to establish some key performance indicators to monitor the impact of the initiative. In fact, impact indicators are essential for many impact assessment methods because they provide a measurable and objective way to assess the impacts.

The ESFRI Policy Brief - Assessment of Impact of RIs refers to different methods for the impact assessment that are summarised as follows:

- Socio-economic assessment based on impact multipliers. The assessment is based on impact multipliers, which estimate the policy's or project's indirect effects on the economy.
- Methodologies applying the knowledge production function. The knowledge production method quantifies the relationship between research and development investment and economic growth.
- Cost-benefit analysis. The analysis considers both quantitative and qualitative factors to make an informed decision. All benefits and costs are expressed in monetary terms, even if the effects are not only financial. Governments and economists often use the approach to evaluate the impact of various investment projects.
- Approaches based on multi-methods, multiple partial indicators. This approach combines multiple methods and indicators to assess the impact of a policy or project. The methods may include surveys, focus groups, and statistical analysis, and the indicators may include economic, social, and environmental factors.
- Theory-based approaches. Theory-based approaches typically share common features, for example, accounting for wider context and external factors that may influence performance, and they define “impact pathways”. The impact pathways approach was further developed in the RI-PATHS project.
- Case studies: This approach involves an in-depth analysis of a particular case to understand the impact of a policy or project. The analysis focuses on the specific context, identifying the factors contributing to success or failure and drawing lessons for future policies and projects.

If the 1+MG initiative considers that it is needed to have proper impact monitoring, one of these methods should be chosen and adjusted to the nature of the initiative and the infrastructure.

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5. Conclusions

Sustainability is a broad concept that should be analysed along the infrastructure design, deployment and decommission. Models to provide funding may differ for the different components of the infrastructure, operations and distribution (central vs decentralised model). As sustainability will depend on the actual structure of the infrastructure, this analysis should be aligned with the elected running structure. Moreover, this cost structure is dynamic, depending on the phase of implementation and development of the infrastructure. In this deliverable, we focus attention to relevant aspects that must be considered when assessing sustainability of the infrastructure and their connotations with the future GDI.

Here, are collected some recommendations and steps for the evaluation of costs, assess the impact of the infrastructure, improve the readiness of the healthcare systems and EHDS, and some suggestions about different funding routes and financial models for the sustainability of the GDI.

6. Next steps

- Define a business model based on the canvas model here proposed.
- To analyse each of the funding programmes to identify specific calls interested for the setup and deployment of the GDI
- Put forward the different financial models and their suitability for the GDI
- To continue the dialogue with the EC and member countries about how they can contribute to the sustainability of the infrastructure (in kind contributions, investment, national and regional funding programmes…)
- Explore the role of the industry in the GDI
- To estimate the cost of the GDI for the central node by defining their services and workflow.
- To estimate the minimum cost to set up a national node (1+MG Data Providers + National Coordination Point) once it is clarified their requirements and workflow.
- To decide the legal entity that will support the setting up of the GDI.
- To establish some impact indicators in order to monitor the social impact of the GDI.

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