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Managing Operating Procedures in Distributed Collaborative Projects

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Abstract. In recent years, large distributed collaborative projects have become very prominent in scientific research, allowing exchanges between laboratories located in different institutions and countries and between various domains of competence. Particularly the work on nanotoxicity – a field which has only been under investigation for a few years and is still lacking regulatory framework – highlighted the need for well-controlled methods, as well as rules for the handling and disposal of used materials. To obtain comparable and reproducible results of experiments conducted in a distributed context, the standardisation and proper documentation of the applied methods is crucial. The European project NanoDiaRA, whose aim is to develop nanoparticles and biomarkers for the early diagnosis of inflammatory disease, faces this situation as it involves 15 European partners and brings together different scientific cultures and professional backgrounds. Protocols especially developed for Superparamagnetic Iron Oxide Nanoparticles and a management system were designed and implemented within the NanoDiaRA project to fulfil those needs. The main goals were the establishment of standardised Standard Operating Procedures assuring transparency and reproducibility and the provision of access to these protocols to every project partner, as well as their clear allocation to carry out precise measurements and production steps.

1. Introduction

Large distributed scientific research projects, involving a large number of scientists from different institutions and scientific disciplines, have become increasingly prevalent in the recent past. In Europe, this is mainly the result of the European Commission's efforts to implement Research Framework Programmes (FP) aiming to foster collaborative links between different research institutions. In addition to the usual Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP) requirements which underlie any research project, large distributed research projects have brought along additional challenges. These can arise from the diversity of geographical and scientific backgrounds, differences in scientific cultures and methods or divergences in institutional approaches and management practices. To this effect it is essential to ensure a flawless exchange of data, methods

and research samples between all the partners involved in such a collaborative project. Particularly it is essential for the following requirements to be fulfilled:

- Manufacturing steps, experimental measurements and production procedures have to be reproducible for every partner.
- Exchange of experimental samples, clinical probes and scientific data must be properly recorded.
- Sensitive samples have to fulfil specific requirements like correct deposition of potentially hazardous materials and appropriate storing. Strict rules have to be followed in line with the regulations of the partner providing the samples, those of the partner receiving the samples as well as the regulations of the project itself.
- Ethical standards have to be adhered to with regard to scientific data and, even more, clinical samples. Again, regulations of all partners involved have to be met.

Another major challenge of distributed collaboration is the effective use and integration of existing information located at the various involved sites. This can be a particularly sensitive problem in the area of clinical studies for which patients are recruited for sample collection and documentation of cases. It requires efficient data management measures to ensure the effective recording, investigating and communicating of the collected information [1]. In addition, the use of human biological specimens in scientific research is also a major issue with regards to bioethics. Collection, handling and subsequent storage of specimens must abide by very strict ethical rules. This is even more complex in the context of collaborative projects where different regulation systems exist. One of the primary concerns is to ensure that the safe and ethical handling of the samples and data security is guaranteed, as well as a proper use and safe disposal of these samples [2].

In the past few years, several institutions have been reconsidering the risk problems of nanomaterials. Many papers have been published regarding their toxicity, but a closer look at the approach showed a lack of proper data and methodology [3][4]. This makes it even more urgent than in other fields to ensure the adequate establishment and communication of methods. In the EU-funded FP7 project NanoDiaRA, partners come from different institutions across Europe and a wide area of diverse scientific disciplines. The project aims at developing nanoparticles and biomarkers to be used for early *in vivo* diagnosis of inflammatory diseases. This requires overall alignment and reproducibility of the various scientific and technological practices in the different research fields. Superparamagnetic Iron Oxide Nanoparticles (SPIONs) are produced by the Laboratory of Powder Technology (LTP) at the Ecole Polytechnique Fédérale de Lausanne (EPFL) and distributed to the other European partners who work in the fields of biology, biotechnology, medicine, physics and microtechnology. The production process of these particles and the exchanges with the other partners in relation to the particle use and the associated methods and results served as a basis to develop clear research protocols and an electronic management system that ensures a proper utilization and documentation of these protocols as well as of the related research samples. The methods which were used to establish the research protocols are described in section 2, followed by the standards put in place for the development and implementation of an electronic management system which are discussed in section 3.

2. Protocols for distributed research projects

2.1. Distributed scientific research

Conducting science within a collaborative context can fertilize research by bringing together people with different expertise, but can also raise several challenges that add to the usual scientific practices. This section explores the context of distributed projects in more depth to justify the need for the setting up of effective research protocols to support collaborations.

Cummings and Kiesler [5] conducted a very comprehensive study of 62 different collaborations – multidisciplinary, cross-institutional and both. They acknowledge that multidisciplinary collaborations are fertile grounds for innovation, i.e., the successful execution of original and inventive ideas and

actions. However, they emphasize that these types of collaborations pose major challenges related to coordination, i.e., the combination of different parts of a project to achieve a common goal. They posit that these challenges are even intensified when in addition the collaboration is cross-organisational. Principal Investigators (PIs) find it difficult to synchronize all the efforts of a consortium of scientific partners who are geographically dispersed and who have different ways of operating. They believe that tighter coordination mechanisms driven by information technologies (IT) have a great potential but that the monitoring of their efficiency is crucial.

Hoekman et al. [6] emphasize distributed research within the European context. They highlight the tension between the benefits of easier cross-border collaborations, which allow the scientists to work together with partners from different countries, and the advantages of cultivating close collaborations which appear to result in more effective research. Jackson et al. [7] go beyond exploring the effect of geographical and institutional dispersion on collaborative research and focus on the temporal dimension. They contend that collaborative scientific work needs to be structured around four temporal rhythms – organizational, infrastructural, biographical and phenomenal – and that in order for the collaboration to operate successfully, additional efforts need to be invested in temporally coordinating the practices of the various partners to align these rhythms.

2.2. *Working with research protocols*

There have been many in-depth explorations of the use of research protocols particularly in the medical field, as medicine is very practice-based but also heavily knowledge- and research-driven. Timmermans and Berg [8] have investigated how the use of very detailed research protocols is embedded within the researchers' working practice. Its development often is a dynamic process that requires multiple interchanges between partners and a string of revisions before establishing the final usable product. Mørk et al. [9] provide a detailed insight of the utilisation of research protocols in various research projects. They thoroughly examine the role of protocols and associated Standard Operating Procedures (SOPs) and identify examples where the production of a research protocol is an individual activity used to carefully track down all the details of the technical operations necessary to conduct an experiment and faithfully document the related technical settings. The emphasis is here on the reproducibility of the scientific operations and on the quality of the experimental work. They also analyse situations in which the development of a research protocol is more of a collective and iterative process which requires in-team and across-team negotiations and the implementation of many adjustments before obtaining a workable document. Finally, they look at these contexts in which the research protocol is part of a much larger structured set of protocols and emphasise the importance of the interlinking of these protocols to support a broader experimental process. The main roles of research protocols in the context of distributed research projects are explored. They can be used to concentrate and bring together the focuses of the researchers, as vehicles for scientific communication and coordination between the various partners, as aide-memoire to pin down the details of the operational procedures to be undertaken during the experimental process, and, finally, as a driver for standardization, interoperability and ultimately quality assurance.

2.3. *SOPs in the NanoDiaRA project*

When NanoDiaRA started in early 2010, operating procedures to synthesise, characterise and manipulate nanoparticles *in vitro* and *in vivo* had already been in use by the different scientists involved in the project. Each contributing research group had its own portfolio with their laboratory requirements in relation to their own competences and domain of expertise.

Similar methods were applied at different locations across the NanoDiaRA consortium, and results were expected to be comparable (e.g., characterisation of nanoparticles, interaction of nanoparticles with living cells etc.). Certain partners provided the nanoparticles or developed new techniques, while other partners had to implement new processes to improve or manipulate these nanoparticles. The same characterisation methods had to be repeated at various time points in the development chain and at different sites to ensure reliability. Therefore, the various results obtained at different stages of this

process had to be recorded, particularly when new methods were implemented. To meet these challenges, identically structured SOPs were established for the project in order to harmonise the different practices across the collaborative project.

A SOP is a protected document which should be shared among partners in different laboratories in order to ensure the reproduction of similar functions, i.e., conducting an experiment, prepare samples, exploit data, prepare administrative documents and send samples [10]. Those *modi operandi* fulfil GLP and GMP requirements to comply with the quality standards expected by the project. This can be done by following basic rules such as shared efficiency of the method and uniformity of the result in compliance with given regulations [11]. The following sections discuss the development process of these SOPs and focus on the particular requirements which have to be fulfilled when producing them.

2.3.1. Participation. The procedure to be implemented for the sharing of SOPs should be established in agreement with all the users involved [12]. In complex research projects, people with different technical backgrounds and scientific cultures may need to make use of the document. Therefore, it has to be understandable by all the collaborators. Any comment made by any members of the consortium who may potentially utilise the protocol has to be taken into account as it may help making it more explicit.

2.3.2. Concision. The content of the SOP should provide sufficient information to be understandable by all the consortium members but at the same time has to be concise enough to provide a maximum of reading clarity [12][13]. Long sentences should be avoided and meaningful examples can be included. The terminology used has to be clear and precise to avoid any unnecessary complexities and thus to allow any reader to get the essence of the protocol without the necessity of further inquiry.

2.3.3. Customisation. Each protocol should be produced in a way that it is possible to tailor it to specific needs and adapt it to different situations. Every individual protocol may have been produced in a certain context but may be reusable in a slightly different one; a certain range of options should be on offer, e.g., “for urine proceed...”; “for organs proceed...”.

2.3.4. Identification. It is essential for SOPs to be unique; only one version must exist at a given time [12][14]. It must not be allowed for different researchers to have separate SOPs for similar but slightly different methods. The aim is reproducibility, and even the smallest variations in the procedure need to be recorded in a leading document, as they may have an impact on the result.

2.3.5. Version management. For traceability reasons, there should be no ambiguity on which version of the document is used for which experiment and at what time point. Each new updated version of a previous protocol should be clearly distinguishable from the previous one to avoid any confusion [12][14].

2.3.6. Qualification/Restriction. For measurements and characterisation methods, limits and ranges must be set: All users should know what specifications are to be expected as a result of this, for example nanoparticles of 40 nm size; no toxicity on cells... [11][15].

2.3.7. Availability/Accessibility. Even if the versions are tightly controlled and regularly updated, all SOPs should be made accessible to all the project partners across the consortium [12][16][17]. This allows the traceability of all experiments, avoids variation among the consortium members and promotes constructive discussions between the collaborators.

2.4. Practicalities of the use of SOPs

One of the NanoDiaRA project partners, the LTP at EPFL, already had SOPs in place when the project started. To extend their utilisation to the rest of the project, they used their expertise, for example for

setting limits of measurement and their previous experience in SOP management to modify the existing documents in order to satisfy the global project needs. New protocols were also implemented to fulfil the consortium's requirements. To meet the new challenges of an extended collaboration, it was essential to develop very clear standardised templates for the protocols as well as a proper file organisation system to effectively manage their use.

2.4.1. Templates. Standardised templates were introduced to ensure that all future generated protocol documents would follow the same pattern to foster concision, consistency and reproducibility. A full reorganisation of the supporting system was then implemented for several purposes: SOP identification and segregation, document version management and access management.

Templates were created in order to facilitate the production of new or already existing procedures so that laboratory technicians and scientists are strongly encouraged to standardise their protocols in a simple and sustainable way. The SOP documents include practical information such as the title, the author's name and the person responsible for its control as well as the date when the SOP becomes effective. A summary provides a quick description of the procedure, i.e., a clear and concise explanation of the aim of this procedure. For a laboratory methodology, a list of materials and machines required for conducting the experiment or making the measurements should also feature.

As part of the technical description of the procedures, all the steps were numbered to allow better readability but also to enable internal referencing – e.g., “8. Repeat steps 1 to 7 twice” – and referencing to laboratory notebook (lab book) entries. These sections have to be filled in with great care and precision and remain concise so that the method is understandable to everyone. The language used is English and the terminology should be carefully selected to describe accurately how to proceed through each of the steps. The use of subsections is highly recommended in order to provide a well structured layout and to clearly separate each of the phases of the documented protocol or method, e.g., 1. Preparation of the sample; 2. Assay; 3. Analysis etc.

An appendix section was also included to provide space for recording complementary information that could be helpful while following the SOP, for example images illustrating a technique, graphs for back calculations, etc. [12]. All pages are numbered and include a reference to the name and version of the SOP.

2.4.2. File organisation. It is crucial to support the development of standardised protocols with a robust and flexible management system to avoid misleading, overlaps, duplications or handling errors [11]. This section discusses the SOP management system which was introduced to accompany the introduction of the unified project operating procedures. A new electronic system was thus designed at LTP to include the following areas: draft version, corrected version, final version and PDF forms to produce a step by step follow-up of the SOP preparation.

When a new SOP form is created, a strict naming convention has to be followed to include the type of SOP – i.e., cell-related; nanoparticles synthesis; human resources etc. –, the SOP number, the version – with a “D” for Draft – and the title, for example “HR 1-2D Arrival of new collaborator”. As soon as the form is completed by the author, it is forwarded to a document control manager who will carry out a first review of this document. At the end of this process, the form is printed out and reviewed by the concerned users who are strongly advised to add comments, as those are essential to improve the quality of the document [11]. All comments and edits, if accepted, are then saved in the updated file and a second revision process takes place until the final version is accepted by everyone; the “D” is subsequently removed from the naming, and the final version is saved. Finally, the operating procedure document is printed out and signed by the author, the document control manager and the supervisor. This paper-based copy is then stored in a ring binder located in the laboratory for general accessibility. This master copy is also scanned and converted into a PDF file to safely keep an electronic version which can be passed subsequently onto other partners. The new version replaces the older one, if existing. The electronic copy of the older version is archived in the “old SOPs” section of the system, while the old paper version is removed from the laboratory. For monitoring purposes, old

versions should be kept in order to be able to track down, for instance, which batch of nanoparticles was produced or which version of the method was used; important changes may have occurred in the SOP which could have affected the result. In addition, to avoid any mix-ups with older versions while new ones are effective, old versions should not be made available to anyone except to the document control manager [12]. Finally, the critical question of the dissemination of the SOP among the consortium partners is considered. It needs to be carefully managed because of the complexity of the collaboration with a high number of dispersed partners in a distributed research context. Once the SOP document is finalised, a satisfactory system with an easy approach should be found to allow anyone to access it and to upgrade the document whenever needed, but still under close supervision.

3. Information Technologies within distributed research projects

3.1. Collaboratories

To overcome the problem of different people at different locations, there have been many attempts to design information technology-driven collaborative platforms. Those are focused on group productivity [18] and on the reduction of the geographical and time-based constraints imposed by large multidisciplinary and cross-institutional collaborative setups. One main area of study has been the conceptual design and sometimes practical development of technology-driven collaboratories, i.e., the idea of an interconnected ever-accessible laboratory in which scientists can interact with each other and access instruments and data irrespective of location and time.

Finholt [19] puts forward a very detailed account of the historical evolution of this concept and provides an in-depth analysis of the opportunities and challenges that the model of collaboratories offers. He contends that even if collaboratories will not change the way science is done, they still represent a very relevant interconnection between digital technologies and resulting changing scientific practices. On one hand, collaboratories and other technological-driven collaboration platforms can enable an increase of influential research partners from various fields, a more efficient sharing of the resources and a more effective combination of observational data with theoretical visualisations. Thus, collaboratories can allow the bridging of the gap between various disciplines and also between theoreticians and experimentalists, shaping scientific practices towards a more multi-dimensional view of the research problem under study. On the other hand, the inherent constraints of the use of a computerised platform can lead to a reduction of the sense of a common global vision and a loss of common ground. Hence, the challenge for the developers is to provide the teams with tools which can counterbalance the diminution resulting from the lack of co-location [20] particularly for tightly coordinating experimental tasks which require frequent interactions and feedback between partners.

3.2. Management of the experimental process

In recent years, many attempts have been made to develop IT tools to support the experimental process at the heart of the work of the scientists. These range from Electronic Laboratory Notebooks (ELNs) which aim at extending the functionality of lab books, to Laboratory Information Management Systems (LIMS) which attempt to integrate the overall documentation of the experimental process [18][21].

Scientists involved in the experimentation as part of a scientific project need to record the experimental practices they undertake. They also need to thoroughly document all the activities which support the experimental process. Mackay et al. [22] offer a detailed account of what the lab book and its potential digital extension represents for the various categories of contributors to a scientific project. For the experimenter, the lab book should be distinguished from the simple production of scratch notes and is used to methodically record and track the experimentation procedures alongside the related observations, analyses and results. Their primary concern is that the lab book should be a universal platform embedded within their scientific practices which can seamlessly support the implementation of experimental operations. In their view, it is a simple and flexible tool which allows

the capturing of meaningful information and its effortless retrieval. It is structured in a chronological manner to provide an accurate temporal account of the “live” tasks which were executed, but can also include some reflective elements when edited at a slightly later stage. In the practice of researchers, it often goes beyond the simple recording of scientific facts – it can assemble a wide range of materials for a variety of purposes such as experimental techniques, spontaneous observations, snippets of data, partial results, external documents and images. For the project management team, the lab book provides the opportunity to monitor the progress of the various members of the project. It is also seen as a centralised and durable repository of essential project information which can be used as evidence for discovery and as the basis for further exploitation.

There has been a tendency to consider IT to support the documentation of the experimental process and thus to implement a set of digital platforms. The latter provide scientific research teams with ubiquitous tools to be used in and out of the laboratory to manage the research-based operations, but also to help coordinate these in a distributed environment. Myers [18] distinguishes between these electronic lab books which are designed to cater for individual needs, and those developed to foster collaboration and support coordination between team and consortium members. Tabard et al. [23] propose an analysis of the functionalities offered by various electronic notebooks and experimental management systems. Schraefel et al. [21][24] make attempts at designing and developing tools which explicitly retain the specificities of the paper media, but extend it to provide additional benefits such as ease-of-use, flexibility and ease-of-share. Tabard et al. [23] stress that a new generation of tools should be considered to provide better support of increasingly complex multi-disciplinary and cross-institutional projects. In their view, the digital laboratory platform should be a central storage space of information, designed to support interactions between the various stakeholders of the scientific projects and networked collaborations between the various members of the research group. It should offer sufficient flexibility to allow the various teams to adopt an organisational strategy which is suitable to their specific needs and practices, and provide a simple means for the involved collaborators to share knowledge, know-how and specific techniques. Finally it should offer mechanisms to keep track of a wide range of heterogeneous physical and digital data such as internal and external written communications, research protocols, ongoing results and experimental samples.

3.3. Development of an Electronic Sample Book for NanoDiaRA

3.3.1. Driving Principles. For NanoDiaRA, several strategies were adopted with the aim to meet the high standards required by such an interdisciplinary project and to ensure the proper management of scientific data and samples. In a first stage, the partners from the different disciplines developed SOPs as described in section 2. An electronic system was initially developed to track the exchange of samples within the project. In a second stage, an internet-driven Electronic Sample Book (ESB) was developed to merge these two areas of functionalities. The idea was to provide all the partners with a documentation system to handle all the samples, methods and protocols used within the project. This should be conducted with a view to ultimately ensure the traceability and reproducibility of each step of the production and each produced result. The goal was to design and develop a tool that is easy to use and that can in principle support any collaborative project, with a heavy focus on fulfilling GMP and GLP requirements as well as ethical regulations. Another important idea was to avoid the necessity of installing the system at the partner institutions and the need of an extensive training of the users, as this would have taken too much time and effort for a time-limited project like NanoDiaRA.

The data produced as part of the project is stored in a structured manner in the ESB by defining the samples as the basic unit of research. Technically, each sample is represented by a database record. Each sample record consists of different fields depending on its type. The sample types, their properties and associated processes for measuring and producing such a sample can be defined by the various involved institutions.

For NanoDiaRA, nanoparticles, MRI pictures, biological samples etc. can be created as records in the ESB. All necessary information is recorded by the users who fill in the essential details for each

specific sample. As the users enter the required information for their specific samples, it is possible to create types for every item that can be recorded and exchanged within a project. Furthermore, one type can be integrated into another (e.g., an MRI picture of an animal, or a biofluid containing particles), thus allowing all the properties of the merged samples to still be traceable. Then any created records can be sent to other groups. To track the shipment of a sample, the *state* property of the record is changed to “on its way”, and the group who is meant to receive it is notified that the sample has been sent. The ESB allows the monitoring of all scientific actions and of their results, helps harmonizing research protocols and prevents loss of samples.

For the purpose of the NanoDiaRA project, particle suspensions were synthesised at LTP and sent to other partners. The group working at EPFL was used as the basis to develop the first prototype of the system and establish proper and useable documentation and sending practices. Each new batch of particles was recorded into the ESB in order to track it and provide the related information. Ranges of acceptance were defined and implemented, thus allowing anyone consulting the database to determine the potential acceptance of the samples. Each sample sent to another location needs to be tracked and followed accurately throughout the process: i.e., the quantity, the properties, its usage and the obtained results. This enables for levels of the various consumables and for the needs of each of the partners to be constantly under control. Finally, essential information regarding samples and other items can be transferred from the databases located at the various partners’ locations and recorded in the ESB.

3.3.2. Fulfilment of GMP, GLP and Intellectual Property requirements. All partners using the ESB can provide their established SOPs and other experimental process descriptions, details of the outputs of the experimental processes, i.e., “sample properties”, an entry for every sample and clinical probe they are sending to or receiving from other project partners, and a description of the production steps, tests or other scientific work that are relevant for the project.

Similarly to a paper lab book, the ESB should ensure that after a result has been filled in once, no further manipulation of this entry is possible. If the properties of a sample need to be edited, the updates have to be entered as the record of a new result. This guarantees that the information provided at a certain time by the person responsible for the sample is accurately documented and is subsequently made available for any potential search in the case of Intellectual Property (IP) related questions. However, in the case of an accidental typography error, there is an option to mark a result as faulty for a certain period of time after it has been filled in. To ensure that everything is recorded, the faulty result is not discarded but appears as crossed out. For all other more significant changes, the administrator has to be contacted and can decide whether a manipulation should be modified or rolled back. Logging every data submission of all users registered in the ESB guarantees the effective monitoring of every action. Manipulations made by the administrator can be hidden to avoid confusion but are still recorded in the system. An independent server provider stores all the data as long as necessary; this is valid beyond the end of the project. Therefore, it ensures proper long term documentation of all information which may become crucial for IP questions that could occur during the project or as a result of the achievements of the project. Data monitoring and security is provided in NanoDiaRA by a subgroup in which academic and industrial partners are informed constantly. A connection with the clinical database at Charité Berlin was established, transferring selected project-relevant parameters as read-only data to the partners. The connection and selection of parameters was conducted in accordance with Charité’s data safety regulation; therefore it serves as a prototype for the integration of internal partner data thus meeting the high standards of a clinical environment.

4. Conclusion and Recommendations

The management of large distributed collaborative projects is a complex process which requires thoughtful planning and organisation. The main focus must be to generate a valuable output of the results gained through the research project. This becomes especially relevant with regards to relatively new fields like nanoparticles and their toxicity. In this new environment, the establishment of methods

and protocols are an evolutive and ongoing task, and the significance and impact of results is still under consideration [25][26].

Modern technologies nowadays have the potential to ease workflows between partners and provide the basis for a complete documentation accessible to everyone at all times. Different electronic systems can be put in place and adopted by all partners at various locations, but this takes time and capacities, raises the risk of safety leaks and jeopardises data protection. In addition, one of the main challenges specific to the NanoDiaRA project was to put in place specific techniques to fit the peculiarity of the materials in use and meet the challenges of a research area which is still lacking standards, as well as to develop clear procedures to handle and eliminate these materials in use in the project. Moreover, a fine line had to be found as it was important not to impose changes which were too radical for the partners involved.

The afore-mentioned challenges can be met by a two-fold approach:

- First, a clear methodology has to be implemented to attempt to unify the methods in place in each collaborating institution. Obtaining standardisation and complete reproducibility of the methods used by every partner can increase the value of the produced results and enhance the overall scientific impact of the project. To enable this harmonisation of methods in one unified methodology, relevant aspects for development and use of SOPs have to be defined.
- Second, flexible electronic information solutions ought to be designed and used to fulfil the specific needs of a distributed collaborative project, in accordance with the standards adopted by all partners involved, as well as GMP and GLP requirements. The focus hence should be on the ease of setting up and using of the system, a clear navigational structure, as well as on the possibility to operate rapid and easy comparisons of the produced results.

Both of these steps are crucial for the establishment of a proper workflow and the generation of comparable and valuable results across the distributed collaborative project. In NanoDiaRA, we made a first attempt to implement them in a structured and explicit way. We hope that the standards that we established will increase the scientific value of the results obtained throughout the lifecycle of NanoDiaRA, and that they can be used as standards for other projects.

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