D3.1 – Definition of data requirements, e-forms, control procedures for data quality, and signed authorisations with different data holders to reuse existing datasets

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Table of Contents

Table of figures

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1. Introduction

The deliverable D3.1 (Definition of data requirements, e-forms, control procedures for data quality, and signed authorisations with different data holders to reuse existing datasets) refers to T3.1 (Access to retrospective data) and T3.2 (Definition of data to be collected and e-form definition) of WP3 corresponding to O3 stated in the DOA. The results of the mentioned tasks cover the work on the access to retrospective data including regulatory, ethical, contractual and administrative tasks related to the use of retrospective clinical data in PRIMAGE project in the context of an observational retrospective trial, and the definition of data to be collected as well as e-form definition. In many aspects the reported results are built on the results of D9.1 and D10.2.

Consider PRIMAGE as an observational retrospective trial this project will use as main sources the retrospective clinical data at a European level, for Neuroblastoma (NB) and Diffuse Intrinsic Pontine Glioma (DIPG), coordinated by their respective European networks. The recent report will explain the formal procedure to request access to data and the responsible entities for the management of the respective registries SIOPE DIPG Registry (DIPG-specific), SIOPEN-r-net registry (NB-specific) and the data repository of the GPOH trials (NB-specific) as well as the use of retrospective data on DIPG and NB from our three clinical partners and two additional imaging biobanks.

Furthermore, this report will describe the specifications for the de-identification/pseudonymisation process to be used in task T3.3 (data extraction and curation), which shall be taken into account in regulatory/contractual tasks.

2. Clinical Data Sources

PRIMAGE project will use retrospective clinical data for training and validation of the in-silico models during developments. These data provide the basis for all the future processes concerning clinical data queries. The access to data for secondary use will serve as foundation for platform validation. So the right way to deal with clinical databases and networks is of great importance for further platform development. This task includes all regulatory, ethical, contractual and administrative tasks related to the use of retrospective clinical data in PRIMAGE project. Furthermore the sources and responsible entities for the management of the respective registries, as well as partners of PRIMAGE, are described.

2.1 PRIMAGE as an observational retrospective Trial

Access to retrospective clinical data

The retrospective study is performed a posteriori, using information on events that have taken place in the past. Most of the data has already been stored in a registry and unlike in prospective studies it does not need to follow patients into the future and therefore often need less time to conduct. Furthermore, in the case of rare diseases such as the present NB and DIPG, a registry allows patients to be pooled from many centres in order to achieve an evaluable study population. Hence, retrospective studies based on real world data (RWD) have an important impact on epidemiological surveillance and disease progression, allowing comparison and evaluation of different treatments and help define prognostic factors, as it will be done for PRIMAGE platform. In the case of PRIMAGE project, access is granted on several registries and clinical trial databases for secondary use of available clinical data. This context is explained in more detail in section 2.2 on data sources and networks.

The further secondary use of clinical trial data must necessarily be done in agreement with the Ethics Committee and highly respecting data protection rules. All project partners providing data submitted the project to their respective Ethics Committees (EC). The EC of the project coordinator (HULAFE) as well as from CCRI have already approved the study. EC approval from UNIPI and UKOELN is still pending although expected soon. Definition and description of signed authorisations is accomplished in section 4.3 on control procedures for data quality.

Regulatory, ethical, contractual and administrative tasks

T3.1 includes all regulatory, ethical, contractual and administrative tasks related to the use of retrospective clinical data in PRIMAGE project.

As referred in D11.1 (Post-Grant Requirement No.1: Research on human being: children) PRIMAGE deals with Real World Data (RWD) from NB and DIPG patients that have already been diagnosed and treated in the different collaborating hospitals, registries and trials to develop the in-silico tumour behaviour prediction models. When working with patients' data, it is mandatory the acquisition of approval from the Ethical Committees concerned in order to extract the relevant patients' data we are considering from their local repositories with a first ethical guarantee step. This approval provides an initial check of the ethical worthiness of the project, and authorizes PRIMAGE to start its data collection undertakings.

PRIMAGE partners' institutions providing data on patients' clinical information are:

1. Universitario y Politécnico La Fe (HULAFE) (as hosting partner of high-risk Neuroblastoma trials (LINES study) and SIOPE DIPG Registry)
2. St. Anna Kinderkrebsforschung - Childrens´s Cancer Research Institute (CCRI) (as hosting partner of SIOPEN trials on high-risk Neuroblastoma)
3. Klinikum der Universitaet zu Koeln (UKOELN) (as hosting partner of the GPOH trials on Neuroblastoma)
4. Universita di Pisa (UNIPI)

Apart from the previously mentioned, there will be other hospitals that albeit they are not official partners, will collaborate with PRIMAGE sharing their data. We have already begun contacts with the main hospitals in Spain that treat patients affected of NB and DIPG. The ethical procedures and regulatory aspects will be held the same way as in HULAFE. In addition, in this Project we will gain access to registries and databases such as SIOPEN-r-net (International Society of Paediatric Oncology European Neuroblastoma Research Network), GPOH (German Society of Pediatric Oncology and Hematology) and SIOPE (European Society for Paediatric Oncology) DIPG registry whose existence is up to clinical trials and other research purposes. To confirm and regulate the collaboration between the different hospitals, registries and databases with PRIMAGE project, there will be signed and recorded collaboration agreements.

In the resolution from HULAFE Ethics Committee (7th of march 2019), informed consent was waived based on the International Ethical Guidelines for Health-related Research Involving Humans Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO) (2016) in which it is stated that:
"A research ethics committee may approve a modification or waiver of informed consent to research if: the research would not be feasible or practicable to carry out without the waiver or modification, the research has important social value and the research poses no more than minimal risks to participants."
In view of PRIMAGE project is a non-interventional study that will design a medical product (a tool to support medical decisions at diagnosis in two paediatric cancer), it was also submitted to the Spanish Agency of Medicines and Medical Devices (AEMPS, Agencia Española de Madicamentos y Productos Sanitarios) and it was classified as "Observational" on the 12th of March 2019.
Once we had the project approval from the research Ethics Committee and the classification as "Observational study" from the AEMPS, data collection activities in the context of the PRIMAGE project were initiated at HULAFE.

To be compliant with the General Data Protection Regulation (GDPR), a report was elaborated by the Legal Area of HULAFE Health Research Institute which justifies the management of personal data in this Project and meets the regulations on data protection both at European and Spanish level. The related legal framework is the General Regulation (UE) nº 2016/679 of Data Protection and the Organic Law 3/2018, of 5th December, in Protection of Personal Data and guarantee of digital rights.

The treatment of health data in Spain is covered by letters g), h), i) and j) of Article 9.2 of Regulation (EU) 2016/679 and the following laws and its development provisions:

a) Law 14/1986, of April 25, General of Health.

b) Law 31/1995, of November 8, on Occupational Risk Prevention.
c) Law 41/2002, of November 14, basic regulation of patient autonomy and rights and obligations regarding information and clinical documentation.
d) Law 16/2003, of May 28, on cohesion and quality of the National Health System.
e) Law 44/2003, of November 21, on the organization of health professions.
f) Law 14/2007, of July 3, on Biomedical Research.
g) Law 33/2011, of October 4, General of Public Health.
h) Law 20/2015, of July 14, on the organization, supervision and solvency of insurance and reinsurance entities.
i) The consolidated text of the Law on guarantees and rational use of 105 medicines and health products, approved by Royal Legislative Decree 1/2015, of July 24.
j) The consolidated text of the General Law on the Rights of Persons with Disabilities and their social inclusion, approved by Royal Legislative Decree 1/2013 of November 29.

In the aforementioned PRIMAGE project, we work with dissociated data instead of personal data. Therefore, no personal data will be stored in the PRIMAGE system and information that can identify the patient is not included.

In the collection of retrospective data, the seventeenth additional provision of Organic Law 3/2018, of December 5th, on the Protection of Personal Data is complied with. Thus, there is a commitment of technical and functional separation between the research team that collects the information in each of the centers and the pseudonymisation team, who will be the only one who will keep all the information and who will make sure that sensitive patient data keeps within the center network. In addition, there is a commitment of confidentiality and non-reidentification, by the research team.

For compliance in the PRIMAGE project of Organic Law 3/2018, of December 5th, on the Protection of Personal Data, the following has been prepared:

1. An evaluation of the impact on data protection with analysis of the risks arising from the treatment including the risks of re-identification of the data.

We have evaluated the ethical risks related to the data processing activities of the project. This includes the evaluation of the impact of data protection as required by the General Data Protection Regulation.

The data of the PRIMAGE platform, as well as its use during the Project are anonymous. People who collaborate with PRIMAGE (platform users, clinicians and radiologists of each of the clinical partners of the project) will be able to enter clinical molecular data, imaging, genetic and other from different hospitals.

2. Together with the impact assessment, security measures that guarantee non-re-identification by researchers, and access to this data by unauthorized third parties have been specified.

Any compilation of patient identities, names or study identifiers will remain on the side of the hospital-institution and will not be known by the entire team of the centralized PRIMAGE repository. There is no personal data that can be accessed and/or manipulated by the participants of the PRIMAGE project within the PRIMAGE platform.

Hospital centers have all the necessary measures to ensure a responsible approach to data management, both for data collection and processing, as well as adequate control and supervision mechanisms. All hospital centers in the project have extensive experience in the management of clinical trials. All use protocols in accordance with their national data protection laws.

In each clinical partner a data administrator will be appointed to ensure that the data is handled ethically and legally. The procedures for data collection, storage, protection, retention and destruction will comply with national and EU legislation. The data administrator and each clinical center will be solely responsible of keeping an internal tracking between the patient codification existing in PRIMAGE platform and the real identity of the patient to guarantee proper coherency of the cases registries

The following data sets are used for PRIMAGE platform tests:

- **Clinical data**. The use of natural language processing tools for automated extraction of relevant pathological data, including data on patient characteristics and phenotypes, will be used from those in the Electronic Health Records (EHR). Next, the data is structured and stored. For

records in handwritten format, the manual entry of the data in the platform forms will be carried out.

- **Image data**. Image data represents the biggest challenge in terms of storage and processing. In the PRIMAGE data repositories, for each patient, the image data is linkable to their anonymous biological, pathological and genetic data. Image analysis techniques are proposed for automated data annotation for each image to generate common repositories.
- **Genetics and other molecular data**. This project uses existing knowledge about biological biomarkers, currently in clinical use or in the advanced clinical validation phase. This type of data is used in combination with images and related clinical data, which facilitates the analysis of large volumes of multidisciplinary data. Currently, clinical data repositories are very fragmented. This is due to the lack of use of common data file structures for different types of data.

In order to standardize the data, in the PRIMAGE project the partners will implement:

1. Protocols for the acquisition and processing of images, for the standardization of data formats for different types of data.
2. Tools to simplify the processes of data extraction, field assignment, data anonymization and dissociation, and in any case, guaranteeing the traceability of the data.
3. A common repository, based on open cloud infrastructure with query data based on semantic annotation.

In order to collect a sufficient amount of data to develop the models required in the PRIMAGE Platform, as long as possible, patient data will be collected from 2002 on, always retrospectively. Approximately, 80% of the data collected from the different institutions will be used for the training and testing of the Platform. The remaining 20% will be used for internal validation of the PRIMAGE Platform.

For the external validation of the PRIMAGE Platform, data from institutions outside the PRIMAGE consortium will be used, with which collaboration agreements will be established in which the same practice is guaranteed in relation to the procedures for data collection, storage protection, retention and destruction, complying with national legislation, Organic Law 3/2018, of December 5th, on the Protection of Personal Data and guarantee of digital and EU rights and the General Data Protection Regulation.

2.2 Data Sources and Data Networks

DATA SOURCES

Hospitals

The tasks of the clinical partners HULAFE, CCRI and UKOELN within the EU-funded project concern the selection of the data set with a sufficiently long observation period as well as the procurement and coding of the imaging procedures. These include the definition of appropriate clinical variables, the definition of imaging modalities, the selection of molecular biomarkers, and the provision of appropriate datasets for the validation of the platform. The access only takes place to already existing data records, which are merged in the sense of the project goal. In the project, no biometric data are used and evaluated, but only pre-existing data records are accessed in compliance with the data protection agreement.

Patient data from hospitals, databases and registries will be incorporated into PRIMAGE platform, which is designed for the purpose of the PRIMAGE project by one of the partners, QUIBIM. It complies with all legal and regulatory aspects in matter of data protection, anonymizing them automatically before being incorporated into the platform.

For the data coming from hospitals, there are two methodologies for data entry:

- Manual data entry to PRIMAGE Platform by the clinicians.
- Automatic data entry to PRIMAGE Platform using Radiomics Enabler®.

Radiomics Enabler® is a web server developed by MEDEXPRIM, which is installed on the hospital's premises and connected to the hospital's PACS (Picture Archiving and Communication System). The

two systems communicate using the DICOM (Digital Imaging and Communication in Medicine) protocol. It is combined with RSNA's Clinical Trials Processor to form an ETL (Extract-Transform-Load) for big data projects in biomedical imaging and it can be integrated within a Clinical Data Warehouse (CDW) to create unified and harmonized patient cohorts, with a complete access to their clinical and imaging data. Image series are extracted and de-identified according to a pre-established set of rules and routed to a research PACS or a post-processing destination inside or outside the hospital using a secured connection. This process is totally automated. For existing databases and registries an automated field mapping will be implemented by QUIBIM, who is the responsible of PRIMAGE database and MEDEXPRIM. Specific scripts will be programmed for this purpose, since they depend on the format of previous registries.
At HULAFE Radiomics Enabler® (a MEDEXPRIM web server) has been installed in order to extract automatically and de-identify the images at diagnosis and after the first treatment evaluation from the patients affected by NB and DIPG that meet inclusion criteria. Images include MRI, CT, mIBG-scans and PET/CT. Digital images from the period 2010 to 2019 are currently available in HULAFE's PACS system.

The formal procedure to request access to data will be initiated during the project and the responsible entities for the management of the respective registries are partners of PRIMAGE. Data from the following registries can be used by PRIMAGE partners for secondary use in the PRIMAGE platform.

Registries and databases

SIOPEN-r-net database

The SIOPEN-r-net (International Society of Paediatric Oncology European Neuroblastoma Research Network) is NB specific and managed by CCRI. It includes clinical, biological and imaging data of high risk NB patients, participants in academia-promoted clinical trials.

The CCRI has the role of the academic sponsor of the international high-risk Neuroblastoma trial (HR-NBL1/SIOPEN, EK-Nr. 115/2006) and will use the data for secondary research purposes.

Clinical trial data of the HR-NBL1/SIOPEN trial have been and will continue to be pseudonymised by the AIT (Austrian Institute of Technology), via EUPID (European Unified Patient IDentifier), a novel pseudonymisation method which will be explained in detail in section 3 about the de-identification and pseudonymisation process. Pseudonymisation is a prerequisite for merging clinical records with associated image data (MRT, CT, PET, mIBG Scans) and further tumour-biological data, while respecting the data protection requirements.

To date, about 3,500 patients have been included in the HR-NBL1/SIOPEN study and the data collection period for the retrospective data analysis covers the years 2002 to 2019. Accordingly, the retrospective data of the HR-NBL1/SIOPEN study from the beginning of 2002 to the autumn of 2019 (end of the study 09/2019) will be used. For a prospective study planned at a later date, an amendment will be submitted in time.

Data repository of the GPOH trials

The data repository of the GPOH trials (GPOH: Gesellschaft für Paediatrische Onkologie und Haematologie - German Society of Pediatric Oncology and Hematology) is NB specific and hosted by UKOELN. In this data repository, clinical, biological and imaging data of low, intermediate and high risk NB patients are captured, amongst them participant of the German national neuroblastoma trials of the GPOH, trial NB97 (NCT00017225), trial NB2004 (NCT00410631) and trial NB2004-HR (NCT03042429).

Data collected within the GPOH data repository will be used for secondary research purposes after ethical approval of the project. To date, data on nearly 2,000 patients of all risk groups diagnosed between 2002 and 2016 (end of recruitment of the trial NB2004-HR) are available.

As discussed above, pseudonymisation is necessary to meet data protection requirements while merging clinical records with associated imaging data and, if available, additional molecular data. The

pseudonymisation process for data of the data repository of the GPOH trials is not finally decided. A pseudonymisation by AIT (Austrian Institute of Technology) via EUPID (European Unified Patient IDentifier) as mentioned above and explained in detail in section 3.1 has been identified as one possible way to be explored.

SIOPE DIPG Registry

The SIOPE (European Society for Paediatric Oncology) Diffuse Intrinsic Pontine Glioma (DIPG) Registry is a comprehensive dataset built from a collaborative collection of clinical, biological and centrally reviewed radiology data of patients with DIPG, both in- and outside clinical trials to allow for international research in the field of DIPG. The SIOPE DIPG Registry was developed based on international agreements, made by a Network of experts studying and treating DIPG; the SIOPE DIPG Network. Initially started as a European network, it has extended to colleagues from all over the world, with participants from Russia, Turkey and Mexico. In parallel, an International DIPG Registry was initiated and developed, which includes patient data from the USA, Canada, Australia and New Zealand. To allow for the inclusion of uniform data, standardized electronic Case Report Forms were developed by the SIOPE DIPG Network, in coordination with colleagues from the International DIPG Registry (managed by Prof. Dr. Sophie Veldhuijzen van Zanten as Expert Advisor in DIPG).

Its main goals are supporting innovative research and ultimately find a cure for DIPG, the better understanding of the biology of DIPG, the development of more effective therapies and new approaches to diagnosis, response assessment and multidisciplinary treatment and follow-up to improve patient outcomes. As a long-term goal, the registry establishes and maintains a highly collaborative, international, hypothesis-driven research infrastructure that can support a wide spectrum of interdisciplinary and translational projects related to DIPG.

DATA NETWORKS

Involvement of the leading European clinical centres

NB (high-risk patients) and DIPG represent some of the most critical paediatric cancers. As usual for rare diseases their treatment is centralised in a very few clinical centres of excellence in each European country. Therefore, it is highly important to cover some of the most prominent European knowledge in Neuroblastoma and DIPG by including only a reduced number of clinical partners in a Consortium that requires a very high level of interdisciplinarity, with expertise ranging from HPC (High Performance Computing) infrastructure, to visual analytics or multiscale simulation.

From the clinical side, PRIMAGE project brings together Key Opinion Leaders in NB and DIPG, belonging to the European Society for Paediatric Oncology (SIOPE), the University Hospital La Fe in Spain (HULAFE, Project Coordinator), Children´s Cancer Research Institute in Austria (CCRI) and the University Hospital Cologne in Germany (UKOELN). This project will use retrospective data on DIPG and NB from clinical partners, which have not yet been incorporated in SIOPE-DIPG (and will be as a result of this project) and for NB patients that were not participant in the SIOPEN clinical trials or in the GPOH trials.

The three Paediatric Oncology Units participants in this project are national reference centres for NB in Spain, Germany and Austria, and they manage the clinical files for these nations´ patients since more than 20 years, as well as biobanks with frozen samples of tumour, bone marrow and blood. Also, there will be incorporation of data from the Pisa oncological imaging biobank (managed by partner UNIPI) and from the Valencia imaging biobank (managed by partner HULAFE-GIBI).

3. De-identification and pseudonymisation Process

Due to regulatory aspects, personalised data which was previously collected in a clinical trial may not be used in a different context without asking the patient for consent again. As described above, such

secondary use of clinical data has a great potential to provide significant new findings from already existing data, which could potentially improve future treatment of children suffering from cancer. The anonymization or pseudonymisation of trial data is a possibility to overcome this regulatory barrier within an appropriate governance framework. However, anonymization inhibits data linking completely, and pseudonymisation of data requires novel concepts of secondary data use in compliance with data protection. This task will include the specifications for the de-identification/pseudonymisation process. In particular, pseudonymisation using EUPID will be considered as one of the options, which shall be taken into account in regulatory and contractual tasks to be used in task T3.3.

3.1 EUPID – European Unified Patient IDentity

In the context of the ENCCA project (European Network for Cancer Research in Children and Adolescents) a so called Virtual Institute (VI), called Integration Domain shall be established to facilitate the exchange of data between source (Source Domain) and consumer (Consumer Domain). The Integration Domain is responsible for storing the data, facilitating data aggregation and providing the aggregated data. Fulfilling technical and organisational requirements as well as legal and data protection issues, Nitzlnader and Schreier 2014 propose an appropriate concept for the ENCCA Patient Identity Management (PIM). Registering the patient under a new identifier (pseudonym) is the creation of a new patient. Requirements for the patient identity management concept are listed in figure 1 (1) (2) (3).

R1	PIM should prevent a duplicate registration of one and the same patient.
R2	Preserve the possibility to re-identify subjects by a trusted third party in special cases, e.g. to inform a patient about relevant research outcomes on-demand.
R3	Different pseudonyms should be used also for one and the same patient for different contexts, e.g. different data sources. However, the PIM should provide a method to link the different pseudonyms in the background to allow secondary use of the data stored within the VI. In other words the PIM concept should provide the ability for the VI to link datasets that belong to the same patient but are stored under different pseudonyms of that patient. At the same time, an identification of patients should be rendered (almost) impossible for another context, e.g. for researchers from institutions that do not know the patient from a treatment context.
R4	Avoid creating a transparent universal patient ID that would impose re-identification threats by the potential availability of an increasing number of linked datasets.
R5	The PIM concept has to be feasible in a distributed computing environment.

Figure 1: Requirements for the patient identity management concept. Nitzlnader M et al. 2014.

In the course of the ENNCA project the Advanced Biomedical Collaboration Domain for ENCCA (ABCD-4-E) has been established to share data between different sources in a distributed computing system. The ABCD-4-E features the European Unified Patient IDentity Management (EUPID) concept that allows registration and pseudonymisation of patients as well as linkage of the different datasets without the need of using directly identifying data elements. After the patient registration the data uploading using the ABCD-4-E network for different contexts takes place. Each context consists of patients and their raw data with context specific pseudonyms (PSNINRG and PSNGEO) and the coordinating researchers. In both contexts the patients were identified using their identification properties (IDAT).

In the course of the PIM process an internal context specific patient ID (PID) is generated from the patient identification properties (IDAT) and a defined context (De-Identification) which subsequently is transformed into a context specific pseudonym (PSN) by using a one-way hashing algorithm (Pseudonymisation). Each context-specific PSN belonging to the same patient is assigned to a virtual and inaccessible PID called ENCCA Unified Patient Identifier (EUPID). Figure 2 illustrates the whole PIM concept.

EUPID and its PRIVACY-PRESERVING Record Linkage (PPRL) addresses two primary challenges that lie at the inter-section of biomedical research and clinical practice: firstly, the de-duplication and linking of datasets for use by researchers, without disclosing the participant's identity; and secondly the

re-identification of research participants for clinical purposes, such as to return results that may be useful in clinical diagnosis or treatment. Data protection and privacy regulations pose increasing challenges to foster networks in and between Biomedical Research and Healthcare and in particular secondary use of data. Recently, PPRL (Privacy-Preserving Record Linkage) via EUPID was acknowledged in a recent paper from the IRDiRC (International Rare Diseases Research Consortium) task force. The PPRL task force concluded that the EUPID approach held the most promise for the emerging, global GA4GH (Global Alliance for Genomics & Health) and IRDiRC research environment. In particular, the task force was impressed with EUPIDs use of context-specific identity attributes, hashing functions, and pseudonyms to locate privacy risks and its use of phonetic hashing to enable robust linking.

EUPID may provide a method to link pseudonyms from different contexts. If needed EUPID enables privacy preserving record linkage but also preserves the possibility for re-identification by a trusted third party. EUPID prevents duplicate registration of patients, avoids publishing a transparent universal patient ID: EUPID may use different pseudonyms for different contexts.

EUPID is recognized by the European Commission as an approved pseudonymisation method for secondary research. Among other things, all Rare Disease Registries will use EUPID as a pseudonymisation pool in the future. The following link refers to the description of the procedure of the European Rare Disease Registry Infrastructure (ERDRI): https://eu-rd-platform.jrc.ec.europa.eu/erdri-description

CCRI therefore decided to add EUPID (European Unified Patient IDentitiy Management) to the existing HR-NBL1/SIOPEN data base. This described pseudonymisation method allows data transfers respecting data protection rules, record and context linkages of clinical data including data from image environments and biomaterials as well as the respective results.

As PRIMAGE was waived the Inform Consent from the patients that will be included in the project, for HULAFE it will not be able to use EUPID with patient data before 2020 because patients information which is not completely anonymized cannot legally leave the hospital environment without inform consent for that purpose. It would be solved submitting the PRIMAGE project with this amendment to the Ethics Committee again and designing the inform consent for patients included from 2020 to 2022.

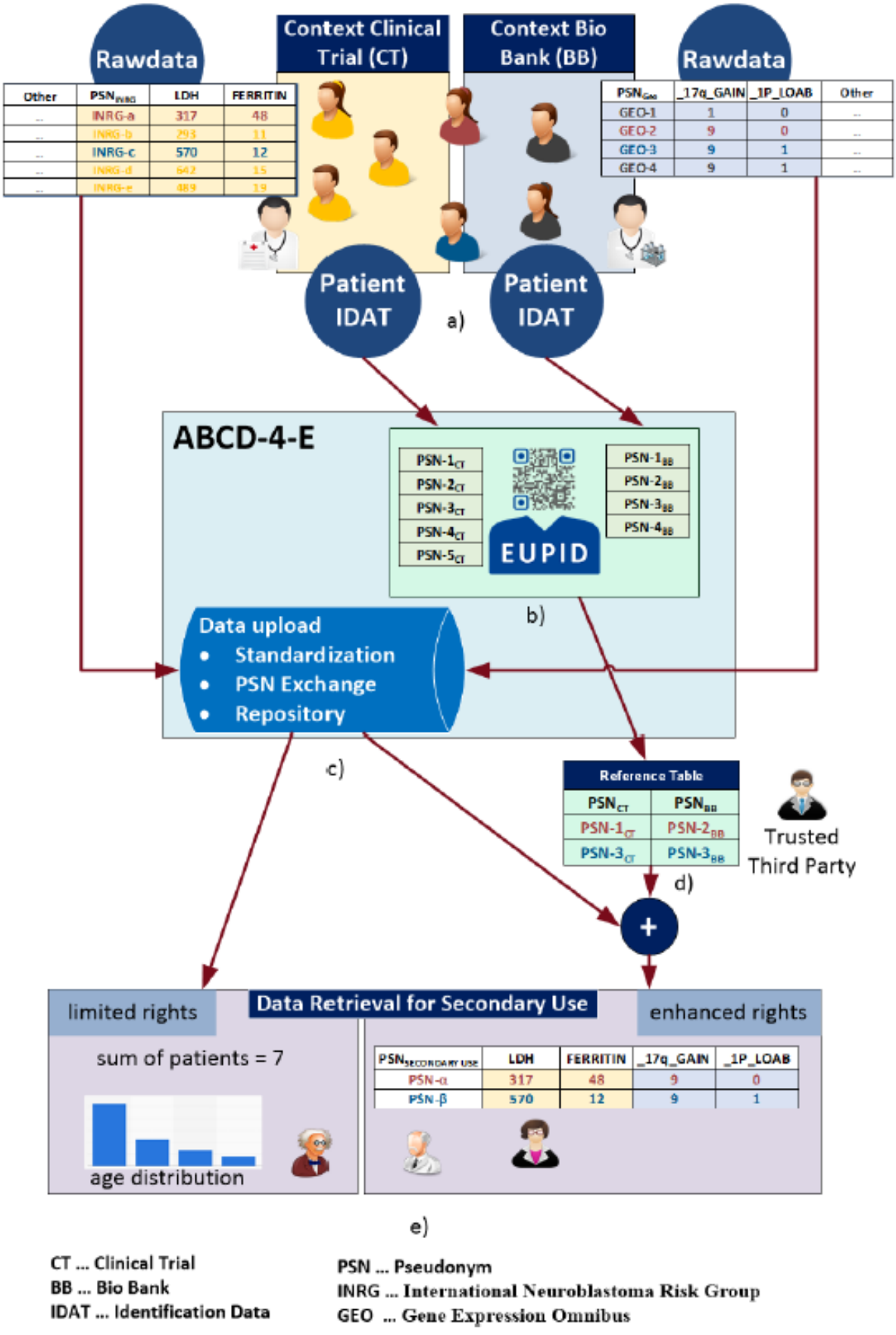

Figure 2: Workflow for patient registration and data upload of clinical trial and biobank data for combined secondary use. Ebner H et al. 2016.

3.2 PRIMAGE Platform anonymization

PRIMAGE platform is going to host all the studies involved in the PRIMAGE project. During the studies uploading process, their anonymization is done. This anonymization is performed in the client site. Therefore, sensible patient data is completely disassociated from the images when uploaded to the cloud storage.

In order for a dissociation procedure to be considered sufficient for the purposes of the regulation, "it will be necessary for the application of such procedure to be impossible to associate the data that is available to a specific subject". This implies that there is no possibility, even remote, that, through the use, prior, contemporaneous or later of any means (computer process, program, system tool, etc.), the information concerning those affected by the processing of data, that is in possession of the consultant, can reveal its identity.

Accordingly, in order to understand that the dissociation has been performed correctly, it is necessary that it is not possible to identify the patient. In order for a dissociation procedure to be considered sufficient for the purpose of the regulation to understand that personal data are not being processed, "it will be necessary for the application of said procedure to be impossible to associate a certain data with a specific subject".

In this sense, the provisions governing the protection of personal data come to the conclusion that the person affected will not be determinable when their identification requires a disproportionate effort that is sufficient to dissuade the person who accesses the data from the identification of the person to whom the same is concerned.

In this regard, platform procedures for the project will follow the following specifications related to the management of dissociated data:

(i) the software incorporated in PRIMAGE platform to eliminate the metadata of the images does not allow the researchers at any time and in any way to have access to personal information. Specifically, the fields ‘Patient Name’, ‘Patient Id’, ‘Study Id’, ‘Patient Birthdate’ are removed from the image header in the user computer before uploading the images to the servers of PRIMAGE platform (DICOM format header).

(ii) the medical professional should not provide for any reason to PRIMAGE platform the patient information that allows any researcher to know the patient's identity. In particular, the only data that PRIMAGE researchers and the clinician must share must be the images themselves together with clinical, pathological and molecular information (without metadata containing personal data of the patient) and the image identification code (not the patient) that PRIMAGE platform must generate before uploading the image. This code should only allow the identification of the images, but not the patient (it is the responsibility of the clinician and the data administrator at each center to relate the code of the image to the patient).

When data of a new subject is incorporated in the PRIMAGE platform using the manual entry way or through Radiomics Enabler®, a new and unique code is given for its anonymization (ie 01-NB-0013, which corresponds to patient 13 from hospital 01 associated to the NB database). To identify the different centers, a unique code will be associated to each one.

When manually entered via the platform portal, the anonymization code to a new patient will be automatically generated by the PRIMAGE platform following the structure described before and ensuring its uniqueness. When uploaded through Radiomics Enabler®, the first digits (ie. XX-NB) will be configured for each given site, and the last digits will be automatically generated by Radiomics Enabler®. It will be a hash of the hospital’s patient unique ID. The user uploading the images will have access to the correspondence table with the original patient ID and the pseudonymized ID, should he need to add clinical data through the portal and need to know which subject to attach them to.

Independently the way used for the anonymization, the data that the rest of researchers and clinicians find in the PRIMAGE platform is the same. In Figure 3 it can be seen an example where three different patients have been included in the PRIMAGE platform after their anonymization. They all have been uploaded by the site with code “02” and have been included in the DIPG project.

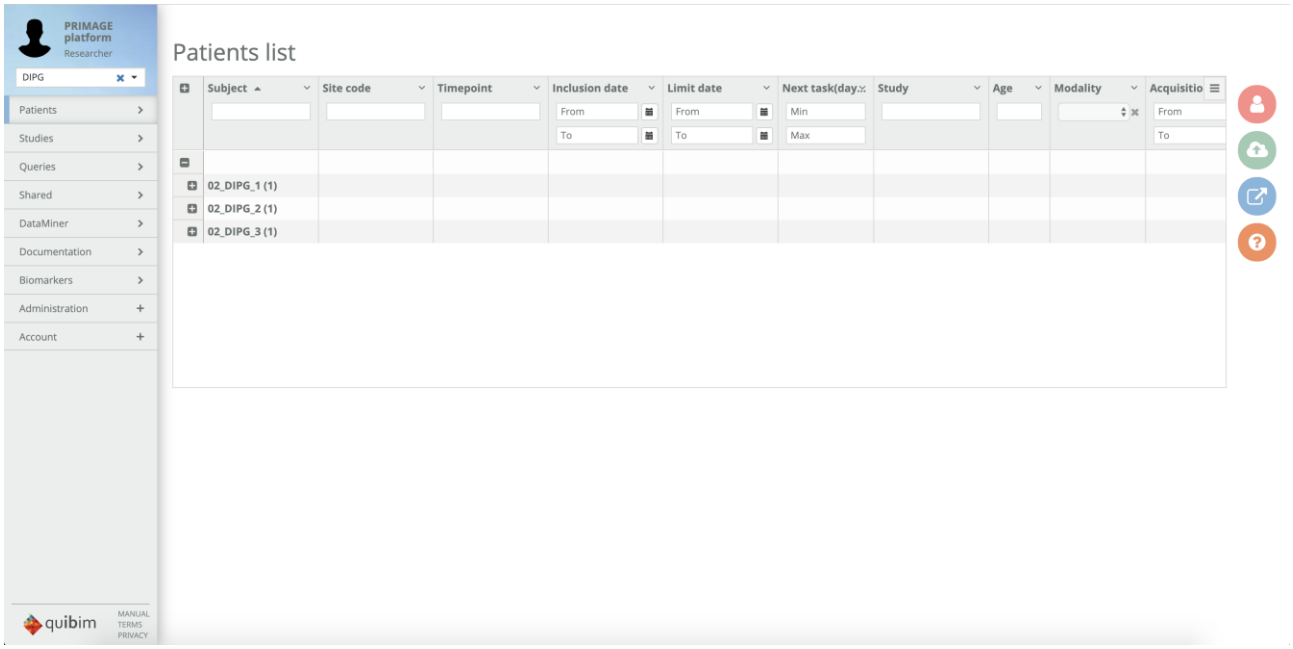

Figure 3. Patient list view in PRIMAGE platform

Finally, PRIMAGE platform allows multiple ways of data entry and specification of patient codification, including:

1. Manual introduction with automatically generated codes (associated to the user affiliation and correlative patient number).
2. Introduction through Radiomics Enabler®.
3. Introduction with EUPID generated patient identifiers
4. Introduction by automated field mapping from pre-existing registries

Detail about the anonymization process using the PRIMAGE platform portal:

Users can add new studies by uploading their images. Study upload process is triggered by clicking in the “Upload study” action button. This action is a three-step process: file selection, anonymization and upload.

After clicking the “upload study” action button, the following window is opened. The first step is to upload to the browser the study DICOM files. Study files (and folders) drag and drop action is available in order to simplify the file upload procedure.

The second step is the anonymization. The anonymization process is done completely in the client browser, DICOM headers are erased in the browser so no sensible information is uploaded to PRIMAGE servers.

The erased DICOM headers are the following:

(0010,0010), Patient's Name, PatientName, PN

(0010,0020), Patient ID, PatientID, LO

(0010,0021), Issuer of Patient ID, IssuerOfPatientID, LO

(0010,1001), Other Patient Names, OtherPatientNames, PN (0010,1002), Other Patient IDs Sequence, OtherPatientIDsSequence, SQ (0010,1005), Patient's Birth Name, PatientBirthName, PN

(0010,2297), Responsible Person, ResponsiblePerson, PN

(0014,2006), Evaluator Name, EvaluatorName, P

(0008,0081), Institution Address, InstitutionAddress, ST

(0040,0006), Scheduled Performing Physician's Name, ScheduledPerformingPhysician Name, PN

(0040,1010), Names of Intended Recipients of Results, NamesOfIntendedRecipients OfResults, PN

(0008,0082), Institution Code Sequence, InstitutionCodeSequence, SQ

(0032,1032), Requesting Physician, RequestingPhysician, PN (0008,0090), Referring Physician's Name, ReferringPhysicianName,

(0008,0092), Referring Physician's Address, ReferringPhysicianAddress, S

(0008,0094), Referring Physician's Telephone Numbers, ReferringPhysicianTelephone Numbers, S

(0008,0096), Referring Physician Identification Sequence, ReferringPhysician IdentificationSequence, S

(0010,1040), Patient's Address, PatientAddress, L

(0040,1010), Names of Intended Recipients of Results, NamesOfIntendedRecipients OfResults, PN

(0040,1011), Intended Recipients of Results Identification Sequence, Intended RecipientsOfResultsIdentificationSequence, SQ

(0040,1012), Reason For Performed Procedure Code Sequence, ReasonForPerformed ProcedureCodeSequence, SQ

(0040,A075), Verifying Observer Name, VerifyingObserverName, PN

(0040,A067), Document Author (Trial), DocumentAuthorTrial, P

(0040,1060), Requested Procedure Description (Trial), RequestedProcedureDescription Trial, LO

(0040,1101), Person Identification Code Sequence, PersonIdentificationCodeSequence, SQ

(0040,1102), Person's Address, PersonAddress, ST

(0040,1103), Person's Telephone Numbers, PersonTelephoneNumbers, LO (0040,2008), Order Entered By, OrderEnteredBy, P

(0040,4037), Human Performer's Name, HumanPerformerName, PN

(0040,2009), Order Enterer's Location, OrderEntererLocation, SH

(0040,A352), Verbal Source (Trial), VerbalSourceTrial, PN

(4008,0102), Interpretation Recorder, InterpretationRecorder, PN

(4008,010A), Interpretation Transcriber, InterpretationTranscriber, PN

(4008,010C), Interpretation Author, InterpretationAuthor, PN

(4008,0114), Physician Approving Interpretation, PhysicianApprovingInterpretation, PN

(4008,0119), Distribution Name, DistributionName, PN

(0008,1048), Physician(s) of Record, PhysiciansOfRecord, PN

(0008,1049), Physician(s) of Record Identification Sequence, PhysiciansOfRecord IdentificationSequence, S

(0008,1050), Performing Physician's Name, PerformingPhysicianName, PN (0008,1052), Performing Physician Identification Sequence, PerformingPhysician IdentificationSequence, SQ

(0008,1060), Name of Physician(s) Reading Study, NameOfPhysiciansReadingStudy, PN (0008,1062), Physician(s) Reading Study Identification Sequence, PhysiciansReading StudyIdentificationSequence, SQ

(0008,1070), Operators' Name, OperatorsName, PN

(0008,1072), Operator Identification Sequence, OperatorIdentificationSequence, SQ (0010,0020)

PatientID

PatientBirthDate

StudyID

For the anonymization of the images, the DICOM header tags of the images that allow to identify the patient are deleted. After deletion, PatientName tag content is replaced by the patient code generated by PRIMAGE platform. Although Patient Birth date is also deleted, since the relevant information from the clinical perspective is the age, the patient age at the moment of diagnosis is calculated and stored in the PRIMAGE database in months.

4. Data Requirements

The retrospective clinical data to be used in PRIMAGE includes Imaging Data for NB and DIPG as well as biological, pathological and genetics data. Defining precisely the data to be extracted from the different data sources and the imaging sequences to be used facilitates the validation and future use of the platform. The present section on Data Requirements discusses the type of data, clinical variables for low-intermediate NB, high-risk NB and DIPG, respective, for designing an e-form to receive the data in the repository. Finally, important control procedures for data quality to be used in PRIMAGE platform will be defined. All results were discussed among the clinical and IT-Developer project partners to come to common conclusions.
As stated in the DOA of the Grant Agreement types of imaging data for NB include anonymized Magnetic Resonance (MR) and 131I-MIBG scintigraphy examinations in DICOM format. For DIPG images to be chosen include anonymized Magnetic Resonance (MR) and methionine PET/CT examinations also in DICOM format. For both diseases, MR data contain high spatial resolution standard T1 and T2 weighted anatomic sequences, diffusion weighted and dynamic contrast enhanced acquisitions. Besides imaging data, available pseudonymised biological, pathological and genetics data sets should be linkable. Clinical variables to be used in the context of patient registration and e-form format will be discussed in section 4.2.

4.1 Clinical Variables

The comprehensive description of performance and usability requirements of PRIMAGE platform is the basis for later use by the end user. The comparison of Case Report Forms (CRFs) from different data bases and clinical trials led the three clinical partners to a consensus of rational clinical variables to be used by PRIMAGE platform in the areas of evaluation of NB and DIPG. The clinical data used for Neuroblastoma is based on different clinical trials for high-risk Neuroblastoma (HR-NB) and low-intermediate risk Neuroblastoma to finally find a match for the most fitting variables:

- two SIOPEN data bases for the low & intermediate risk neuroblastoma patients (LINES trial with HULAFE acting as international data center)
- high risk patients (HR-NB1/SIOPEN trial with the CCRI acting as international data centre)
- UKOELN university hospital (data repository of the GPOH trials for low, intermediate and high risk neuroblastoma, currently captured on a different data base with a different data base structure)

To achieve a consistent presentation and possibility for case comparison, it is important to establish meaningful clinical variables that will be used to assess each case of disease. We defined variables for each risk group shown in Figures 4 and 5.

NB - Low-Intermediate Neuroblastoma

	Low-Intermediate NB LINES	Low-Intermediate NB UKOELN GPOH
I. PATIENT- AND DISEASE CHARACTERISTICS AT DIAGNOSIS		
Patient		
	Date of birth (ddmmyyyy)	Date of birth (ddmmyyyy)
	Sex (FEMALE/MALE)	Sex (FEMALE/MALE)
	Date of diagnosis	Date of diagnosis
Associated symptoms at diagnosis		
	Spinal cord syndrome (yes/no)	Spinal cord syndrome (yes/no)
	OMS (opsoclonus-myclonus syndrome) (yes/no)	OMS (opsoclonus-myclonus syndrome) (yes/no)
LDH		
	LDH result IU/L	LDH result IU/L
	Clinically significant (Yes/no)	pathologic / ambiguous / normal
Primary tumor side		
	Abdominal adrenal (left, right)	Abdominal adrenal (left, right)
	Abdominal other	Abdominal other
	Cervical	Cervical
	Pelvic	Pelvic
	Thoracic	Thoracic
	Unknown	Unknown
	Others	Others
Metastasis		
	Bone (yes/no)	Bone (yes/no)
	Bone marrow (yes/no)	Bone marrow (yes/no)
	Liver (yes/no)	Liver (yes/no)
	Lymph nodes (yes/no)	Lymph nodes (yes/no)
	Skin (yes/no	Skin (yes/no
	Orbita (yes/no)	Orbita (yes/no)
	CNS (yes/no)	CNS (yes/no)
	Lung (yes/no)	Lung/Pleura (yes/no)
	Other (yes/no and free text)	Other (yes/no and free text)
IDRF (Image defined risk factors)		
MIBG		
	Date of examination (yyyy-mm-dd)	Date of examination (yyyy-mm-dd)
	Uptake in the primary tumour site	Uptake in the primary tumour site
	Uptake in the skeleton	Uptake in the skeleton
Bone marrow		
	Aspirate (yes/no, positive/negative)	Aspirate (yes/no, positive/negative)
Other metastasic sites		
	Other metastatic sites yes/no	Other metastatic sites yes/no
	Liver yes/no	Liver yes/no
	Skin yes/no	Skin yes/no
	CNS yes/no	CNS yes/no
	Pleura/Lung yes/no	Pleura/Lung yes/no
Histology (INPC)	histology (INPC) at inital diagnosis	histology (INPC) at inital diagnosis
Status N-MYC		
	FISH (not amplified/gain/amplification)	FISH (not amplified/gain/amplification)
SCA		"-1p, -11q"
NCA		no information
Staging		
	INRGSS (International Neuroblastoma Risk Group Staging System)	INRGSS (International Neuroblastoma Risk Group Staging System)
II. TREATMENTS		
Treatment evaluation: information on given treatments		
First treatment		
	Date of initiation	Date of initiation
Pre-surgery		
		observation / surgery only / chemotherapeutic treatment yes/no; number and kind of cycles
	After CO (yes/no and number of cycles)	
	After VP/Carbo (yes/no and number of cycles)	
	After CADO (yes/no and number of cycles)	

III. DISEASE STATUS AFTER EACH TREATMENT ELEMENT		
Disease status is evaluated more than once and for each time point the status is given as compared to the diagnostic evaluation		
Time-Points		
Primary Tumor response		
	Complete response	Complete response
	Partial response	Partial response
	Stable disease	Stable disease
	Progression	Progression
Metastatic response		
	Metastatic response (CR , PR, SD, PD)	Metastatic response (CR , PR, SD, PD)
Global response		
	Complete response	Complete response
	Partial response	Partial response
	Minor response (regression)	Minor response (regression)
	Stable disease	Stable disease
	Progression	Progression
IV. OUTCOME		
Progression		
	Yes/no	Yes/no
	Date of first relapse	Date of first relapse
	Number of relapses	Number of relapses
	Type of first relapse (local/distant/combined)	Type of first relapse (local/distant/combined)
Regression		
	Yes/no	Yes/no (for patients not treated with chemotherapy)
Current status		
	Alive/death	Alive/death
	Cause of death (progression/toxicity/others)	Cause of death (progression/toxicity/others)
	Date of death	Date of death
	Date of last visit	Date of last visit

Figure 4: Clinical Variables for low/intermediate NB based on LINES trial.

NB - High-Risk Neuroblastoma

For the ongoing work on the definition of the performance and usability requirements of PRIMAGE platform and their descriptions, variables and field names within the HR-NBl1/SIOPEN data base were identified and transmitted to WP partners to agree on a common strategy by comparing data set variables form the SIOPEN LINES trial as well as the GPOH neuroblastoma data base. HR-NBl1/SIOPEN was created by AIT, capturing patient- and disease characteristics at diagnosis, treatments, disease status after each treatment element and outcomes. After comparing variables from the different trials, we agreed on the most important ones shown in figure 5.

	CCRI - SIOPEN HR-NBL1	HULAFE - proposal - HR-NB	UKOELN - HR-NB
I. PATIENT- AND DISEASE CHARACTERISTICS AT DIAGNOSIS			
Patient			
	Sex (FEMALE/MALE)	Sex (FEMALE/MALE)	Sex (FEMALE/MALE)
	Date of diagnosis (DDMMYY)	Date of diagnosis (DDMMYY)	Date of diagnosis (MMYY)
	Age of diagnosis (auto-calculated)	Age of dianosis (auto-calculated)	Age of dianosis (auto-calculated)
Primary tumor site			
	Abdominal adrenal (RIGHT, CENTRAL, LEFT)	Abdominal adrenal (RIGHT, CENTRAL, LEFT)	Abdominal adrenal (RIGHT, LEFT)
	Abdominal other (RIGHT, CENTRAL, LEFT)	Abdominal other (RIGHT, CENTRAL, LEFT)	Abdominal other (RIGHT, CENTRAL, LEFT)
	Cervical (RIGHT, CENTRAL, LEFT)	Cervical (RIGHT, CENTRAL, LEFT)	Cervical (RIGHT, CENTRAL, LEFT)
	Pelvic (RIGHT, CENTRAL, LEFT)	Pelvic (RIGHT, CENTRAL, LEFT)	Pelvic (RIGHT, CENTRAL, LEFT)
	Thoracic (RIGHT, CENTRAL, LEFT)	Thoracic (RIGHT, CENTRAL, LEFT)	Thoracic (RIGHT, CENTRAL, LEFT)
	Other (YES/NO and free text)	Other (YES/NO and free text)	Other (YES/NO and free text)
Metastasis			
	Bone (YES/NO)	Bone (YES/NO)	Bone (YES/NO)
	Bone marrow (YES/NO)	bone marrow (YES/NO)	Bone marrow (YES/NO)
	Liver (YES/NO)	liver (YES/NO)	Liver (YES/NO)
	Lymph nodes (YES/NO)	lymph nodes (YES/NO)	Lymph nodes (YES/NO)
	Lung (YES/NO)	Lung (YES/NO)	Lung (YES/NO)
	Other (YES/NO and free text)	Other (YES/NO and free text)	Other (YES/NO and free text)
Staging			
	INSS (International Neuroblastoma Staging System)	INSS (International Neuroblastoma Staging System)	INSS (International Neuroblastoma Staging System)
MYCN-amplification			
	Fish (NOT AMPLIFIED/GAIN/AMPLIFICATION)	Fish (NOT AMPLIFIED/GAIN/AMPLIFICATION)	Fish (NOT AMPLIFIED/GAIN/AMPLIFICATION)
II. TREATMENTS			
First treatment			
	Date of initiation (start of cycle 1)	Date of initiation (start of cycle 1)	Date of initiation (start of cycle 1)
	Treatment evaluation: information on given treatments	Clinical trial (yes/no)	Treatment according to trial: NB97 vs. NB2004-HR
After induction (Response Evaluation time-point 1)			
	Type of induction: (Rapid Cojec/N7/other)	Type of induction: (Rapid Cojec/N7/other)	NB97 - NB 2004 standard - NB2004 experimental - other
End of treatment			
	Date of end of treatment	Date of end of treatment	Date of end of treatment
III. DISEASE STATUS AFTER EACH TREATMENT ELEMENT			
Metastatic response			
Skeleton (Bone)	SIOPEN MIBG (BONE: Complete response/Partial response/Stable disease/Progression)	SIOPEN MIBG Bone (FDG-PET imaging in MIBG non-avid tumors) (Complete response/Partial response/Stable disease/Progression)	mIBG_Me (pathologic / ambiguous / normal)
Bone Marrow (Trephines & aspirates sepately)	Number of positive sites & number of sites	(Complete response/Minimal disease/Stable disease/Progression)	KM_ZYT (bone marrow cytology) (pathologic / ambiguous / normal)
Other metastatic sites	(Complete response/Partial response/Stable disease/Progression)	(Complete response/Partial response/Minor Response/Stable disease/Progression)	(complete remission/very pood partial remission/partial remission/mixed response/stable disease/progression/relapse/not involved)

IV. OUTCOME			
Progression/relapses (Yes/No)			
	Date of first relapse / progression /second malignancy	Date of first relapse / progression /second malignancy	Date of first relapse / progression /second malignancy
Current status			
	Status (ALIVE/DEATH)	Status (ALIVE/DEATH)	Status (ALIVE/DEATH)
	Cause of death (progression/toxicity/others + free space)	Cause of death (progression/toxicity/others + free space)	Cause of death (progression/toxicity/others + free space)
	Date of death	Date of death	Date of death
	Date of last visit	Date of last visit	Date of last visit

Figure 5: Common Clinical Variables for high-risk NB based on HR-NB1/SIOPEN trial and GPOH database.

DIPG

In case of DIPG variables definition, the process was initiated at HULAFE with CRFs of SIOPE DIPG registry as examples and help. They have been supervised by one member of the advisory board, expert in DIPG and Project Scientific Manager of the SIOPE DIPG registry itself.

After this process, the following variables have been decided to be the main important for the purposes of this project:

Patient data: date of birth, sex and country.

Diagnosis: date (MRI image), age at diagnosis, time from the first presenting symptoms to diagnosis, symptoms (headache, nausea, vomiting, squint, abnormal eye movements, head tilt, focal motor weakness, seizures, difficulty speaking, difficulty swallowing/coughing after eating/drinking, drooling, facial nerve palsy, other cranial nerve palsies, abnormal gait and coordination difficulties, abnormal sensation of face and limbs, behavioral change, school difficulties, pathological laughter, anxiety, tiredness, weight loss, other signs/symptoms), findings in physical examination (pyramidal tract signs: mono-, hemi-, or quadriparesis/plegia; hyperreflexia; or positive Babinski reflex. Cerebellar signs: dysmetria, ataxia, dysarthria, nystagmus. Diplopia. Sensory loss. Cranial nerve palsy (II, III, IV, V, VI, VII, VIII, IX, X, XI, XII).

- Tests: laboratory (CSF (positive/negative for disease) and radiology (MRI Brain with date, type of contrast, spectroscopy done or not done; Spine MRI date, type of contrast, evidence or not evidence of disease; PET-CT with date and findings, brain CT with date and type of contrast).

- Existence of obstructive hydrocephaly and drain technique carried out (external ventricular drain, hird ventriculostomy or entriculo-peritoneal shunt).

- Pathology data from a biopsy in case it has been performed (date, type of sample, reason for biopsy, location of biopsy, number of biopsies, WHO Grade (low grade I-II/high grade III-IV/unknown), pathology diagnosis (pylocitic astrocytoma, fibrillary astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, oligodendroglioma, PNET, Ependymoma, other, unknown).

- Molecular studies: mutation of BRAF-V600E, mutation ofH3F3A (H3.K27M), mutation of HIST1H3B C/I (H31K27M), mutation of ACVR1, mutation of TP53, mutation of ATRX, mutation of TERT, mutation of DAXX, amplification or mutation PDGFRA and others (For the long term survivor ATM, BCOR, BCORL1, PI3CA, PIK3R1, MYC, MYCN, MET, EGFR, NTRK1, NTRK2, NTRK3, NF1, CDKN2A, CDKN2B, CCND1, CCND2, CCND3, CDK4, CDK6, PPMID). Mutations of histones are assessed by Sanger sequencing, whole exome sequencing, whole genome sequencing, polymerase chain reaction, or immunohistochemistry.

- CSF cytology (type of sample (lumbar puncture, ventricular, unknown) and result for malignancy).

Treatment: received under a clinical trial or not and under which one, date of initiation, type (RT that can be hypofractionation, normofractionation, hyperfractionation, unknown and total dose; steroids and its length with temporal relation to RT; chemotherapy (general cytotoxic drugs) timing, drugs, total dose and schedules; bevacizumab and target treatment timing, cycles, total dose; surgery (date and extent); tumor vaccines (dates, type, number).

Evaluation of treatment response (done after first treatment):

- Clinical response evaluation (reported signs/symptoms and findings on physical and neurological examination), date and type of response (stable disease/unchanged, progression, partial response, complete resolution of symptoms, unknown).

- Image: MRI/CT Brain (date, type of contrast, evidence of metastases), MRI/CT spine date, type of contrast, evidence of disease, new hydrocephalus present or worsening of prior hydrocephalus.

- Radiological response: primary tumor (stable disease, progression (refractory tumour, recurrent tumour, second primary tumour, unknown) minor response, partial response, complete response) and metastases (stable disease, progression (the same as in primary tumor), minor response, partial response, complete response.

Follow up: progression (refers to the worsening or spread of disease within the body) date, number of progressions, symptoms; relapse (refers to the return of disease after a period of improvement) date,

number of progressions, symptoms and current status (alive and date of last visit or death and date of death and cause of death (disease related, treatment related, other, unknown).

4.2 E-Form

E-forms are created using simple HTML (Hypertext Markup Language) templates styled using CSS (Cascading Style Sheets) that can be incorporated in PRIMAGE platform. The variables previously specified by the clinicians have been translated to HTML fields. In the user interface, clinical, pathology and molecular-genetics data can be introduced in the same e-form within a patient environment. The variables were specified by their name, their format and the units of measure if appropriate. This guarantees that all registries introduced in the database will keep the same format, maximizing data consistency.

Neuroblastoma NB

The e-form has been divided into 5 main sections: patient data, diagnosis, treatment, treatment response and follow-up. With this structure the access to concrete variables is eased. In some sections (i.e. diagnosis and treatment) additional subsections have been defined. This has been done to avoid large pages which could render their readability difficult.

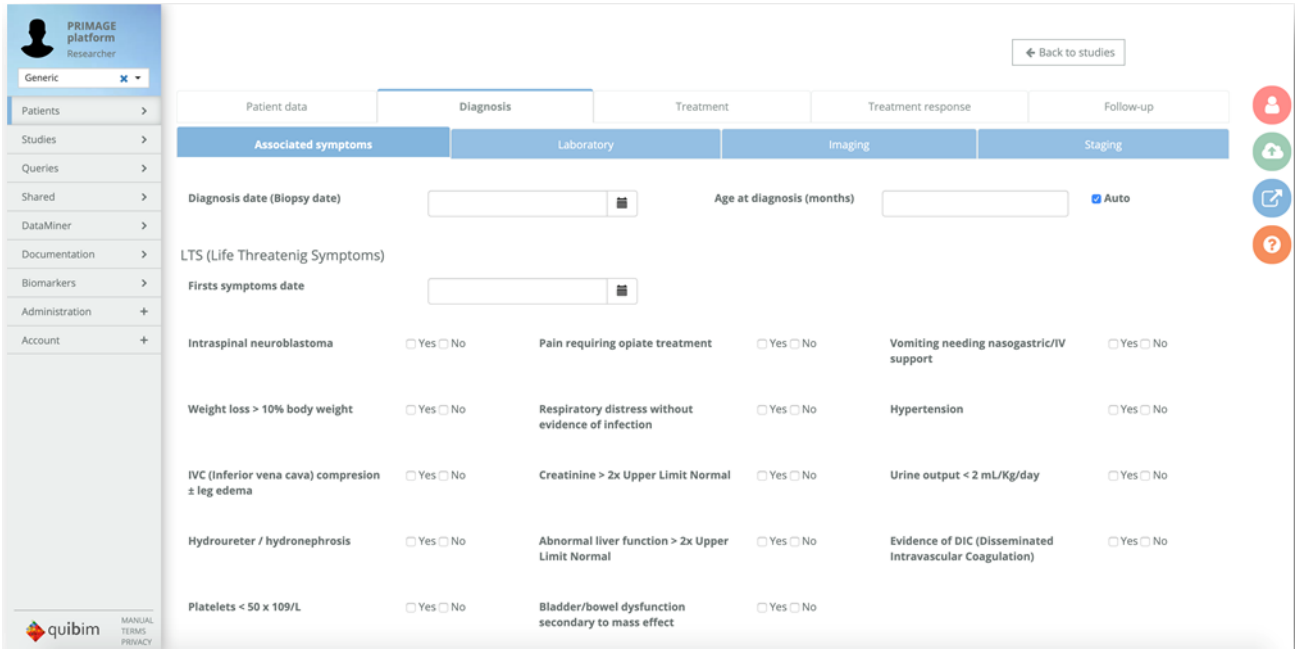

Figure 6: NB e-form. In the upper regions it can be seen the main sections. In the diagnosis sections if can be found some additional subsections where the different variables to fill are defined.

Diffuse Intrinsic Pontine Glioma DIPG

The e-form associated to DIPG patients is currently under construction. It will follow the same structure as the one designed for NB. As defined in section 4.1 (Clinical variables), it will contain the same main sections defined for NB patients. However, the variables included on each would be the appropriate ones for DIPG patients.

4.3 Control Procedures for Data Quality

To ensure the quality of the data incorporated to the PRIMAGE platform through the e-form, different questions, related to the data quality dimensions, should be answered with positive response:

- **Validity: Are all data values within the values domains?**

To ensure the validity of the introduced data different constraints and checks are done:

- Data format: Each value associated to each variable in the e-form has a specific format, i.e. number, string, boolean… Other data types would not be allowed to be incorporated.

- Data range:
  - Texts: when possible define all the definitions of a concrete variable to avoid different names to refer to the same things. These possibilities are defined in a dropdown to select the appropriate one:

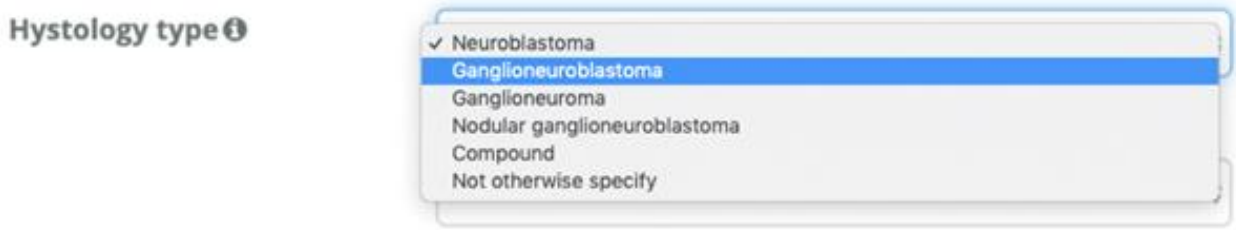

Figure 7: Example of a variable with different text possibilities.

  - Numbers: there are some numerical variables that must have a value within a minimum and a maximum value. For example, the SIOPEN score for NB patients must have a value between 0 and 72 (4) (5). If a number outside these limits is included, it will be automatically removed showing a warning message.

- Data type: There are some numerical variables that require integer values (no decimal numbers are allowed) (i.e. SIOPEN score). In these fields the introduction of the '.' character is not allowed. If this character is introduced because the variable has been filled automatically, a warning is shown in the PRIMAGE platform for its review.

- **Accuracy: does data reflect the real-world objects or a variable source?**

  All the data incorporated into PRIMAGE platform come from different hospitals and official registries to ensure that all the developments performed within the PRIMAGE project have been designed using RWD.

- **Consistency: is data consistent between systems? Do duplicate records exist?**

  To avoid duplicate records, the PRIMAGE platform checks that in the database there are no registries with the same values for the different variables. In the same way, when an image is uploaded to the platform, using the metadata in the DICOM header, it is checked that the concrete image series has not been uploaded previously.

  If any of these inconsistencies are detected, a warning is thrown to the user for its review.

- **Integrity: are the relations between entities and attributes consistent?**

  To ensure the integrity of the introduced data, some fields have to ensure some requirements. For example, in NB patients, the date of the first treatment initiation must be earlier than the date of the images acquisition. If this happens, a warning is generated in the PRIMAGE platform for its review.

  Additionally, for each patient, all the data coming from the e-form is associated with other data coming from different sources (i.e. images, results from analysis, radiomics analysis…).

- **Completeness: is all necessary data present?**

To ensure that all the fields have been reviewed and filled, if any variable has not been collected it is not allowed to leave it empty, it is mandatory to indicate that it has not been recorded.

Figure 8: Example of variables that have not been collected. No additional information is shown if a "no" has been set.

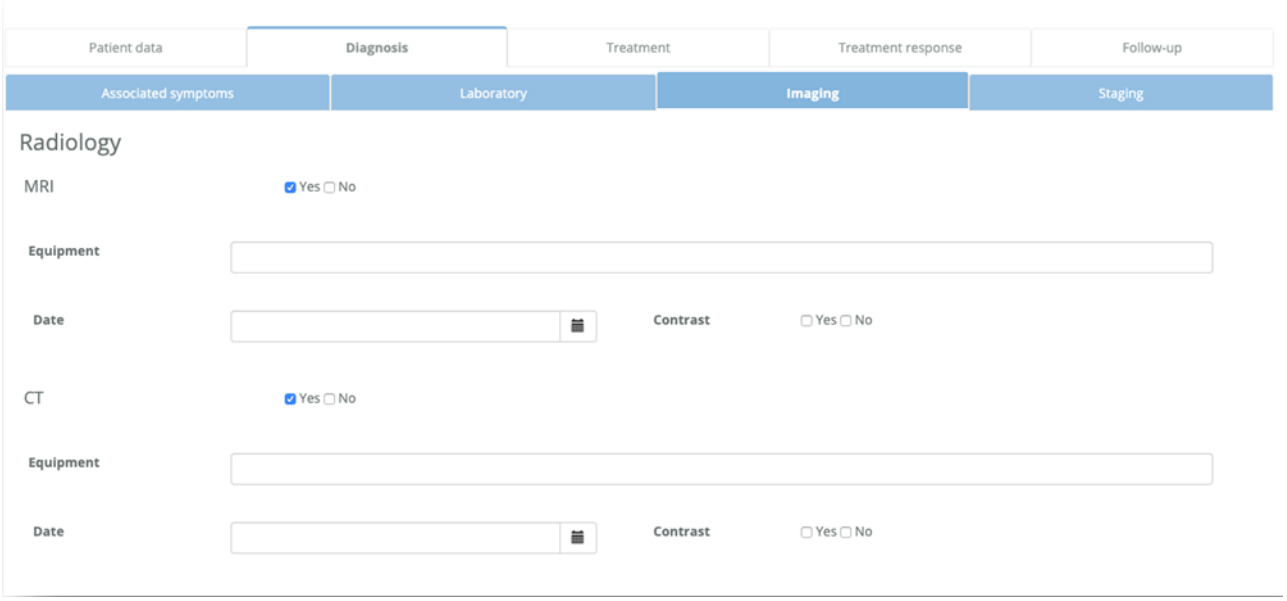

Figure 9: Example of variables that have been collected. Associated additional information is shown when clicking in "yes".

Additionally, all the warnings generated in the previous checks have to be corrected by the data responsible of each centre. If any warning is not reviewed and corrected, the whole study would not be set as *complete.* Moreover, all the radiological images associated to a concrete patient have to be uploaded to the platform. If there are no images uploaded, the study would not be set as *complete*.

5. CONCLUSION

The main challenge was to identify the most meaningful clinical variables because every clinical partner has a different idea on type and especially number of variables to be used. Therefore, we tried to compromise and identify the common ones. This work was done by discussing the contents within a teleconference and by creating Excel-Sheets with tables for comparison as it is shown in tables X.

Subsequently to the definition of the main clinical variables, the clinical markers to be extracted from the existing databases into PRIMAGE platform within WP3 and the molecular biomarkers within WP4 will be discussed. A further discussion going in the direction of data upload was to decide on type, number and age of image data as well as pseudonymisation and time point of upload. IT-partners are optimistic to handle every kind of data just to fill the platform for initial progression. For integrating clinical user questions into PRIMAGE platform as a relevant factor we maybe will have to discuss methods and conditions of digital circumstances with our IT-partners. This topic will be part of WP4.

The Project has an important social value as its outcome will be a decision support tool which will help on a more accurate diagnosis; prognosis and therapy follow up in these diseases. Moreover, as the

research implies in-silico data management and analysis and no interventional activity will take place on the patients themselves, there are no risks to participants.

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7. Acronyms and Abbreviations

Acronym	Definition
EC	Ethics Committee
NB	Neuroblastoma
DIPG	Diffuse Intrinsic Pontine Glioma
SIOPEN-r-net	International Society of Paediatric Oncology European Neuroblastoma Research Network
GPOH	German Society of Pediatric Oncology and Hematology
SIOPE	European Society for Paediatric Oncology
CIOMS	Council for International Organizations of Medical Sciences
WHO	World Health Organization
AEMPS	Spanish Agency of Medicines and Medical Devices
GDPR	General Data Protection Regulation
EHR	Electronic Health Records
DICOM	Digital Imaging and Communication in Medicine
RSNA	Radiological Society of North America
ETL	Extract-Transform-Load
CDW	Clinical Data Warehouse
PACS	Picture Archiving and Communication System
MRI	Magnetic Resonance Imaging
CT	Computed Tomography
PET	Positron Emission Tomography
mIBG	MIBG (Metaiodbenzylguanidin)-Szintigraphy
AIT	Austrian Institute of Technology
EUPID	European Unified Patient IDentifier
HPC	High Performance Computing
ENCCA	European Network for Cancer Research in Children and Adolescents
VI	Virtual Institute
PIM	Patient Identity Management
PPRL	Privacy-Preserving Record Linkage
IRDiRC	International Rare Diseases Research Consortium
GA4GH	Global Alliance for Genomics & Health
CRF	Case Report Form
CSS	Cascading Style Sheets

ANNEX 1: HULAFE Ethics Committee favourable resolution

La Fe
Departament de Salut

FPNT-CEIB-04 (B)

DICTAMEN DEL COMITÉ DE ÉTICA DE LA INVESTIGACIÓN CON MEDICAMENTOS

Dña. María Tordera Baviera, titular de la Secretaría Técnica del Comité de Ética de la Investigación con medicamentos del **Hospital Universitario y Politécnico La Fe,**

C E R T I F I C A

Que este Comité ha evaluado en su sesión de fecha **27 de marzo de 2019**, el Proyecto de Investigación:

Título: **"PRIMAGE. PREDICTIVE IN-SILICO MULTISCALE ANALYTICS TO SUPPORT CANCER PERSONALIZED DIAGNOSIS AND PROGNOSIS, EMPOWERED BY IMAGING BIOMARKERS."**
Nº de registro: **2018/0228**
Versión/fecha de la memoria del proyecto: **07 de marzo de 2019**
Versión/fecha de la Hoja de Información al Paciente y Consentimiento Informado: **Se aprueba la solicitud de exención del Consentimiento Informado.**

Que dicho proyecto se ajusta a las normativas éticas sobre investigación biomédica con sujetos humanos y es viable en cuanto al planteamiento científico, objetivos, material y métodos, etc, descritos en la solicitud, así como la Hoja de Información al Paciente y el Consentimiento Informado.

En consecuencia, este Comité acuerda emitir **INFORME FAVORABLE** de dicho Proyecto de Investigación que será realizado en el Hospital Universitario y Politécnico La Fe por el/la **Dr. / Dra. Luis Martí Bonmatí** del servicio/unidad/grupo de investigación de **RADIOLOGÍA** como Investigador Principal.

Que el CEIm del Hospital Universitario y Politécnico La Fe, tanto en su composición como en sus procedimientos, cumple con las normas de BPC (CPMP/ICH/135/95) y con la legislación vigente que regula su funcionamiento, y que la composición del CEIm del Hospital Universitario y Politécnico La Fe es la indicada en el anexo I, teniendo en cuenta que, en el caso de que algún miembro participe en el estudio o declare algún conflicto de interés, no habrá participado en la evaluación ni en el dictamen de la solicitud de autorización del estudio clínico.

Lo que firmo en Valencia, a 27 de marzo de 2019

Fdo.: Dra. María Tordera Baviera
Secretaria Técnica del Comité de Ética de la Investigación con medicamentos

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

agencia española de medicamentos y productos sanitarios

DEPARTAMENTO
DE MEDICAMENTOS
DE USO HUMANO

DESTINATARIO:

Dª VANESSA SEGURA CABALLER
ONCOLOGÍA PEDIÁTRICA
TORRE G. 2ª PLANTA
HOSPITAL UNIV. Y POLITEC. LA FE
AV. FERNANDO ABRIL MARTORELL, 106
46026 – VALENCIA

Fecha: 12/03/2019

REFERENCIA: ESTUDIO PRIMAGE

ASUNTO: NOTIFICACIÓN DE RESOLUCION DE CLASIFICACIÓN DE ESTUDIO CLÍNICO O EPIDEMIOLÓGICO

Adjunto se remite resolución de clasificación sobre el estudio titulado **"PRedictive In-silico Multiscale Analytics to support cancer personalized diaGnosis and prognosis, Empowered by imaging biomarkers"**

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

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13/03/2019 13:02:48

El acuse de este registro se ha almacenado en el MSCBS (https://sede.mscbs.gob.es)

CSV: VG6JD-DXL2T-VP53H-BEUBX

Agencia Española de Medicamentos y Productos Sanitarios
Fecha de la firma: 12/03/2019
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28022 MADRID

ANNEX 2: CCRI Ethics Committee Vote

ethik kommission
Medizinische Universität Wien

Borschkegasse 8b/6
1090 Wien, Österreich
T +43(0)1 404 00-21470, 22440
F +43(0)1 404 00-16900
ethik-kom@meduniwien.ac.at
http://ethikkommission.meduniwien.ac.at/

Votum:

EK Nr: 1637/2019
Projekttitel: PRIMAGE: Prädiktive In-Silico-Multiskalen-Analytik zur Unterstützung der personalisierten Diagnose und Prognose von Krebs mithilfe bildgebender Biomarker
Antragsteller/in: Frau Univ. Prof. Dr. Ruth Ladenstein
Institution: St. Anna Kinderkrebsforschung
Sponsor: HULAFE Fundación para la Investigación del Hospital La Fe de la Comunidad Valenciana

Teilnehmende Prüfzentren:

Ethik-Kommission	Prüfzentrum	Prüfärztin/arzt
Ethikkommission der Medizinischen Universität Wien	St. Anna Kinderkrebsforschung	Frau Univ. Prof. Dr. Ruth Ladenstein

Die Stellungnahme der Ethik-Kommission erfolgt aufgrund folgender eingereichter Unterlagen:

Conflict of Interest

Name	Version	Datum
Conflict_of_Interest_Antragsteller	V1.0	29.05.2019

Covering Letter

Name	Version	Datum
Cover Letter PRIMAGE	V1.0	29.05.2019
Cover Letter ergänzende Erklärungen	1.0	21.08.2019

Lebenslauf (CV)

Name	Version	Datum
CV WIEN Ruth Ladenstein_2019	1.0	12.03.2019

Sonstige

Name	Version	Datum
PRIMAGE_Ethics Evaluation	V1.0	20.07.2018
PRIMAGE_Consortium Agreement_draft_12_03_2019	V1.0	12.03.2019
PRIMAGE_Ethics Committee Dictum_HULAFE	V1.0	27.03.2019
WP11_PRIMAGE_D11.1	V1.0	31.05.2019
WP11_PRIMAGE_D11.3	V1.0	31.05.2019
WP11_PRIMAGE_D11.4	V1.0	31.05.2019
Schreier et al. 2016. EUPID. Health Informatics Meets e Health. Volume 223	V1.0	04.06.2019

Studienprotokoll (Prüfplan)

Name	Version	Datum
EU Projekt Teil 1 PRIMAGE_24-04-2018_final	V1.0	24.04.2018
EU Projekt Teil 2 PRIMAGE_24_04_2018_final	V1.0	24.04.2018
Engl RL PRIMAGE_Project description for Ethics Committee approval	V1.0	03.06.2019
Rollenbeschreibung CCRI PRIMAGE_310719_V1	V1	31.07.2019

Die Kommission fasst folgenden Beschluss (mit X markiert):

X	Es besteht kein Einwand gegen die Durchführung der Studie. ACHTUNG: Unter Berücksichtigung der "ICH-Guideline for Good Clinical Practice" gilt dieser Beschluss ein Jahr ab Datum der Ausstellung. Gegebenenfalls hat der Antragsteller eine Verlängerung der Gültigkeit rechtzeitig zu beantragen.

Ergänzende Kommentare der Sitzung am 02.07.2019:

Da die eingeladene Antragstellerin nicht an der Sitzung teilnehmen kann, wird der Tagesordnungspunkt unbehandelt vertagt.
Die Prüfärztin wird für die Sitzung am 30.07.2019 erneut eingeladen.

Ergänzende Kommentare der Sitzung am 30.07.2019:

Der Ethik-Kommission liegen derzeit die umfangreichen Unterlagen des Gesamtprojekts vor, aus denen nur schwer herauszulesen ist, wie genau die Beteiligung des lokalen Studienzentrums geplant ist. Aus diesem Grund ersucht die Ethik-Kommission um Vorlage eines Dokuments (Protokolls), welches die Beteiligung der St. Anna Kinderkrebsforschung klar und eindeutig darstellt.

Zur Versicherung:

Die Ethik-Kommission hält fest, dass der Abschluss einer Versicherung für diese Studie nicht erforderlich ist.

Andere: Frau Univ.Prof.Dr. Ruth Ladenstein stellt die Studie persönlich vor.

Die Ethik-Kommission ersucht die Antragsteller, bei der Wiedervorlage von geänderten Unterlagen ein Exemplar mit hervorgehobenen Änderungen beizulegen.

Ergänzende Kommentare:
Nachtrag vom 29. August 2019:
Die Antragsteller legen am 21.08.2019 überarbeitete Unterlagen vor, die von der Ethik-Kommission akzeptiert werden.

Die aktuelle Mitgliederliste der Ethik-Kommission ist unter folgender Adresse abrufbar:
http://ethikkommission.meduniwien.ac.at/ethik-kommission/mitglieder/

Mitglieder der Ethik-Kommission, die für diesen Tagesordnungspunkt als befangen anzusehen waren und daher laut Geschäftsordnung an der Entscheidungsfindung/Abstimmung nicht teilgenommen haben: **keine**

Dieses Dokument ist für berechtigte Benutzer/innen in digitaler Form unter folgender Adresse abrufbar:
https://ekmeduniwien.at/vote/17571/download/

ANNEX 4: Clinical HR-NBL variables according to databases and registries (GPOH, HR-NBL1/SIOPEN) from clinical partners

	CCRI - SIOPEN HR-NBL1	HULAFE - proposal - HR-NB	UKOELN - HR-NB
I. PATIENT- AND DISEASE CHARACTERISTICS AT DIAGNOSIS			
Patient			
	Date of birth (ddmmyyyy) • Sex (FEMALE/MALE) • Hospital principal	Date of birth (dd/mm/yyyy) (will be hided once introduced, just to calculate age at doagnosis)	GEBDATUM (TTMMJJJJ)
	Sex (FEMALE/MALE)	Sex	GESCHLECHT (W/M)
	Hospital principal		
	Date of diagnosis	Date of diagnosis	DIAGNOSEDATUM (TTMMJJJ)
	Age of diagnosis (auto-calculated)	Age of dianosis (auto-calculated)	PAT_ALTER
LDH			
	Units in the data base are problem! - inconclusive	Upper normal value IU/L	
		Lower normal value IU/L	
		LDH result IU/L	
		Clinically significant (Yes/no)	
Primary tumor site			
	Abdominal adrenal (RIGHT, CENTRAL, LEFT)	Abdominal adrenal	LOKPT (=1; adrenal)
	Abdominal other (RIGHT, CENTRAL, LEFT)	Abdominal other	LOKPT (=3; abdominal/midline)
	Cervical (RIGHT, CENTRAL, LEFT)	Cervical	LOKPT (=5; cervical)
	Pelvic (RIGHT, CENTRAL, LEFT)	Pelvic	LOKPT (=6; pelvis)
	Thoracic (RIGHT, CENTRAL, LEFT)	Thoracic	LOKPT (=4; thoracic/ mediastinal)
	Other (YES/NO and free text)	Other	LOKPT (=8; other) + free text
Metastasis			
	Bone (YES/NO)	Bone (YES/NO)	LOKME (=2)
	Bone marrow (YES/NO)	bone marrow (YES/NO)	LOKME (=1)
	Liver (YES/NO)	liver (YES/NO)	LOKME (=4)
	Lymph nodes (YES/NO)	lymph nodes (YES/NO)	LOKME (=3)
	Lung (YES/NO)	Lung (YES/NO)	LOKME (=7; Lung, Pleura)

	Other (YES/NO and free text)	Other (YES/NO and free text)	LOKME (=8; other) + free text
			LOKME (=11) orbita
			LOKME (=5) skin
			LOKME (=10) CNS
			LOKME (=6) Intracranial
			LOKME (=12) skull
Staging			
		INRGSS (International Neuroblastoma Risk Group Staging System)	
		International Neuroblastoma Risk Group Pre-treatment Classification Schema (only for recent patients)	
	INSS (International Neuroblastoma Staging System)	INSS? (International Neuroblastoma Staging System)	INSS
MYCN-amplification			
	Southern (NOT AMPLIFIED/AMPLIFICATION)		WERT (>=5 amplified; < 5 not amplified)
	Fish (NOT AMPLIFIED/GAIN/AMPLIFICATION)	FISH (not amplified/gain/amplification)	WERT (>=5 amplified; > 1 and < 5 gain; 1 = not amplified)
	PCR: (NOT AMPLIFIED/AMPLIFICATION)		WERT (>=5 amplified; < 5 not amplified)
	SNPa, WGS (NOT AMPLIFIED/GAIN/AMPLIFICATION)	SNPa	
Status Genes			
	NAG, DDX, ALK, others (amplification yes/het/no)	NAG	
	ALK (mutation yes/no)	DDX1	
	ATRX, others (deletion yes/no)	ALK (amplified or not)	
	TERT (breakpoint yes/no)		
Ploidy			
	diploid/aneuploid/tetraploid	diploid	

		tetraploid	
ALK mutation (yes/no)			
Segmental chromosomal alterations (SCA)	*-1p, +1q, +2p, -3p, -4p, -11q, +17q, others	"-1p, +1q, +2p, -3p, -4p, +11p, -11q, +17q, others	
MRD (minimal residual disease)			
		Not done	
Bone Marrow	will be available for some patients please contact SIOPEN MMG group	TH	
		DCX	
		PHOX2B	
		DCt-TH	
		Log-TH	
		DCt-PHOX2B	
		log-PHOX2B	
Peripheral Blood		TH	
		DCX	
		PHOX2B	
		DCt-TH	
		Log-TH	
		DCt-PHOX2B	
		log-PHOX2B	
Bone marrow immunocytology (including AIPF)	SIOPEN bone marrow immunocytology group: head: Klaus Beiske		
bone marrow aspirates	at each response time point: cpm/10e6 MNC (cells per million mononuclear cells) and (yes/no)		
II. TREATMENTS			
First treatment			
	Date of initiation (start of cycle 1)	Date of initiation	Treatment according to trial: NB97 vs. NB2004-HR

		Clinical trial (yes/no)	Zeitpunkt (Date of cycle 1 Chemotherapy)
Treatment evaluation: information on given treatments			
After induction (Response Evaluation time-point 1)			
	Date of first cycle		Zeitpunkt (Date of cycle 1 Chemotherapy)
	Date of last cycle		Zeitpunkt (Date of last cycle Chemotherapy prior to other treatment elements)
	Number of cycles given		number of cycles
	Type of induction: (Rapid Cojec/N7/other)	Type of induction: (Rapid Cojec/N7/other)	NB97 - NB 2004 standard - NB2004 experimental - other
After TVD (Response Evaluation time-point 2)			
	Date of first cycle of TVD		nicht zutreffend für GPOH-Studien
	Number of cycles given		
Surgery			
	Date of surgery		Zeitpunkt
	Results on primary tumour (Biopsy/Complete excision/Complete excision - possible microscopic tumour residue/Macroscopic/Resection not possible)		RADPT (0: not specified, 1: sample excision, 2: macroscopically incomplete; 3: microscopically incomplete, 4: macro and micro complete, 5: macro complete and micro unclear, 8: procedure without tumour removal)
After HDT (Response Evaluation time-point 3)			
	Date of ASCR		ZEITPUNKT
	Type of HDT: (BUMEL/CEM/other and free text)		Type of HDT: MEC / BUMEL / other
After Radiotherapy (Response Evaluation time-point 4)			
	Date of radiotherapy		Zeitpunkt
After MRD-treatment (Response Evaluation time-point 5)			

	Date of first cycle		Zeitpunkt
	Date of last cycle		Date of last cycle
	Type of MRD-treatment: (Retinoic acid/GD2+IL2/ GD2)		Retinoic acid/ GD2 / other
	Number of cycles given		Number of cycles given
End of treatment			
	Date of end of treatment	Date of end of treatment	
III. DISEASE STATUS AFTER EACH TREATMENT ELEMENT			
Disease status is evaluated more than once and for each time point the status is given as compared to the diagnostic evaluation			
	Time-Point: (i.e. after induction/after TVD/after HDT/after Radiotherapy/after MRD)		NR (may vary according to trial; examples for NB2004-HR) 0=initial 1=after initial surgery 2=after 2 CT 3=after4 CT 4=after6 CT 5=after8 CT 6= nach HDT 7=after Retin 1 8=vor Retin 2 9=after Retin2 and all follow ups
	Date of evaluations		
Primary Tumour			
	Primary tumour site response (pre/post-Surgery) (Complete response/Partial response/Stable disease/Progression)		ERGEBNIS (complete remission (10 or 11), very poor partial remission (30), partial remission (20,21), stable disease (50,51), progression/relapse)
Metastatic response			

Skeleton (Bone)	SIOPEN MIBG (BONE: Complete response/Partial response/Stable disease/Progression)	SIOPEN MIBG Bone (FDG-PET imaging in MIBG non-avid tumours) (Complete response/Partial response/Stable disease/Progression)	mIBG_Me (pathologic / ambiguous / normal)
Metastatic soft tissue response	in "other mets" text field	(Complete response/Partial response/Stable disease/Progression)	
Bone Marrow (Trephines & aspirates separately)	Number of positive sites & number of sites	(Complete response/Minimal disease/Stable disease/Progression)	KM_ZYT (bone marrow cytology) (pathologic / ambiguous / normal)
Liver	(Complete response/Partial response/Stable disease/Progression)	(Complete response/Partial response/Stable disease/Progression)	.
Other metastatic sites	(Complete response/Partial response/Stable disease/Progression)	Type of global response (INRC) (entered to data-base) (Complete response/Partial response/Minor Response/Stable disease/Progression)	ERGEBNIS (complete remission (10 or 11), very poor partial remission (30), partial remission (20,21), mixed response (40), stable disease (50,51), progression/relapse)
Conclusion metastatic response	mCR, mPR, mSD, mPD	mCR, mPR, mSD, mPD MIBG (CR, PR, SD (=NR), PD)	
Type of global response (INRC) (entered to data-base)	(Complete response/VGPR/ Partial response/Stable disease/Progression)		
IV. OUTCOME			
Evaluated periodically			
Progression/relapses (Yes/No)			
	Date of first relapse progression	Date of first relapse	Date of first relapse / progression /second malignancy
	Type of first relapse (LOCAL/DISTANT/COMBINED)	Type of first relapse (local/distant/combined)	
		Number of relapses	
Current status			
	Status (Alive/death)	Alive/death	STATUS (=1 death; not 1 alive))
	Date of death	Cause of death (progression/toxicity/others)	TODESDATUM
	Cause of death (free space)	Date of death	TODESURSACHE (categories + free text)
	Date of last visit	Date of last visit	LETZT (last visit)