PRIMAGE

Medical imaging
Artificial intelligence
Childhood cancer research

D8.1 – Readiness to start recruitment for clinical tests

Project Full Title: *PRedictive In-silico Multiscale Analytics to support cancer personalized diaGnosis and prognosis, Empowered by imaging biomarkers.*
Project acronym: *PRIMAGE*
Project type: Horizon 2020 | RIA (Topic SC1-DTH-07-2018)
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Reviewer 2	Barbara Hero	UKOELN	OK/NOK

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Table of Contents

Tables & Figures Index

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The opinions stated in this report reflects the opinions of the authors and not the opinion of the European Commission.

Acknowledgement

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1. Introduction

The deliverable D8.1 (Readiness to start recruitment for clinical tests) refers to task 8.1 (Study preparation & regulatory aspects). The results on this task cover the work of setting up all preparation and regulatory aspects to start recruitment for independent data (clinical, biological and imaging) to validate externally the PRIMAGE platform as a tool to predict tumor behavior at diagnosis in neuroblastoma (NB) and pontine diffuse intrinsic glioma (DIPG).

This project will undertake two phases in order to achieve its main objective, develop the PRIMAGE platform as a tool to predict tumor behavior in NB and DIPG in the routine clinical practice.

Phase I: Training, Testing and *In silico* Internal Validation (performed in WP3).

- Training: during this phase the parameters will be extracted to build the predictive models on a cohort of cases. In-silico predictive models to estimate clinical evolution in this first phase will be constructed from the 80% of the data of those patients with a confirmed diagnosis of NB studied between 2002 and 2019. In this series, cases without imaging, biological or genetic relevant studies to the diagnosis will be excluded (clearance) as well as those presenting relevant comorbidities (such as malformations or other neoplasms). From their images, different computational parameters (radiological and dynamic) will be obtained with which to build estimating models of clinical evolution through statistical, multivariate analysis and groupings, from the images obtained at diagnosis and in the first evaluation after starting treatment.
- Testing and *In silico* Internal Validation: subsequently, the clinical predictive model developed will be tested (with 10% of data) and internally validated (with other 10% of data) with cases collected between 2002 and 2019.

Phase II: *In silico* External validation.

- With external and independent cases data from 2002 to 2022, it will be carried out a verification to confirm *in-silico* the potential universality of the model as a decision support system.

Thus, WP8 overall corresponds to O8 of sect.1.1 stated in the DOA, and the main objectives are:

- To validate the platform performance with a dataset cohort of patients different from the one used for training and internal validation in WP3, as a non-interventional study, aimed to demonstrate PRIMAGE platform as a useful tool in routine clinical practice.
- To test the platform usability by the Clinical Partners acting as users of the platform. They will be assisted as well by a technical expert, in order to discriminate usability aspects (which refinement should be subject of future innovation projects and validated in prospective clinical trials) from performance issues which are this project´s core.

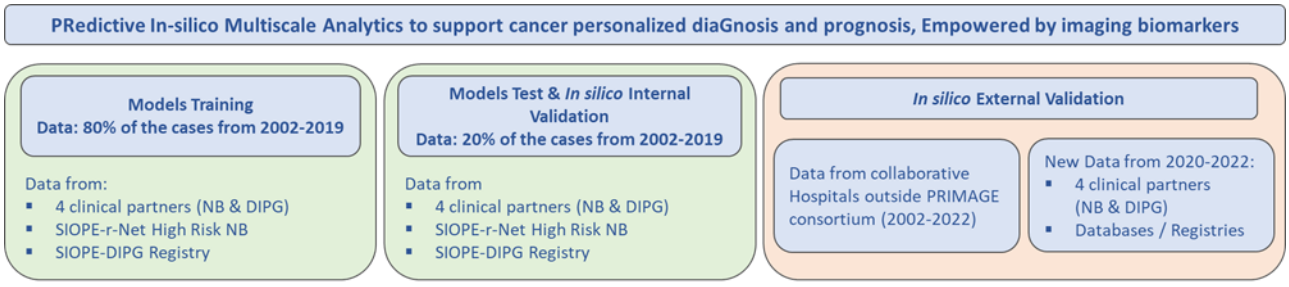

Figure 1. PRIMAGE Development. Green boxes represent Phase I and Orange box represents Phase II.

Table 1. Relevant Acronyms

AEMPS	Agencia Española de Medicamentos y Productos Sanitarios
AEPD	Agencia Española de Protección de Datos
CCRI	St. Anna Kinderkrebsforschung - Children Cancer Research Institute
DIPG	Diffuse Intrinsic Pontine Glioma
EC	European Commission
GDPR	General Data Protection Regulation
HULAFE	Hospital Universitario y Politécnico La Fe
LOPD	Ley de Ordenación y Protección de Datos
NB	Neuroblastoma
PI	Principal Investigator
SIOPE	European Society for Paediatric Oncology
UKOELN	Klinikum der Universitaet zu Koeln
UNIPI	Universita di Pisa

2. Need of an External Validation

The key aspect of PRIMAGE project is to develop an open cloud-based platform with the integration of quantitative imaging data with clinical and biological data to get *in-silico* models to support decision making in the clinical management of two paediatric cancers, NB and DIPG.

The *in-silico* models (made by computers) are fostered by the availability of high throughput datasets and new data analysis strategies. PRIMAGE Project will work with retrospective Real World Data (RWD) from already treated cases of NB and DIPG to build algorithms using new imaging biomarkers. Computer training with these new biomarkers will lead us to generate reliable predictions as well as new knowledge on the mode we stratify neuroblastoma´s patient risk before start treatment or in the way we manage DIPG. But to generate those algorithms and to make computers learn them to be able to see its usability with artificial intelligence we need multiple cases.

Contrary to prospective studies and research controlled data in which there is a homogenous and controlled sample, the main advantages of retrospective studies that use data from the real world (RWD) are slightly different. A retrospective study offers a large population in defined and simple groups, the inclusion of comorbidities and the possibility of having a large temporal window to follow-up patients and their outcome or obtaining real world evidence (RWE). Several disadvantages may be data heterogeneity and a major need to control data quality whereas in the prospective studies and research controlled data there may be limited size groups, the need of more precise inclusion criteria and limited evidence due to subsampling bias and they may take more time.

Nevertheless, in general in science and in particular in research, reproducibility still remains an important issue and it should be the best possible. It is why we need to increase the acquisition of independent NB and DIPG data cases to test *in-silico* the prediction models that will be developed in the training, testing and internal validation phase in an independent cohort.
The *in silico* external validation in PRIMAGE project will be done with different datasets: retrospective data from hospitals outside PRIMAGE consortium and with data from new diagnosed and treated cases of NB and DIPG from PRIMAGE clinical partners and Databases/Registries (see Figure 1). In the latest, cases provided will have a minimum time of follow-up that will be acquired in a prospective way, once we have validated the PRIMAGE prediction tool.

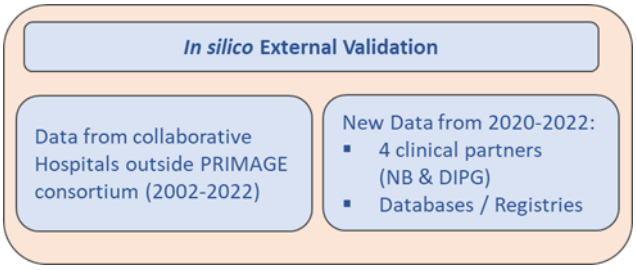

Figure 2. Sources of data for in silico external validation

3. Sources of independent data

Task 8.1 is devoted to detail the steps and all regulatory aspects needed to get independent data from NB and DIPG patients for the external validation. These independent data will be incorporated to the PRIMAGE repository through PRIMAGE platform from European Registries and European hospitals outside the Consortium with historical cases and from the PRIMAGE Clinical Partners and Databases/Registries with new cases, collected from their local repositories. In figure 2 you can see the different sources of data that will be used for the in silico external validation.

Therefore, it will be established collaborations between PRIMAGE project coordinator (HULAFE) and different European hospitals and existing International registries (i.e. International DIPG registry) that are not partners of PRIMAGE. The formal procedure to request access to data has already been initiated and the responsible entities for the management of the respective registries and electronic clinical histories from collaborating hospitals will comply with the relevant regulatory approvals needed (see D11.2).

3.1 Data from External Hospitals

Here is described the steps followed to engage external hospitals in Europe to participate in PRIMAGE project providing NB and/or DIPG cases for the in silico external validation:

Spanish hospitals

In a first step the PRIMAGE project coordinator (HULAFE) has approached 14 Spanish hospitals that treat patients diagnosed of NB and DIPG sending a first letter the 11th of April 2019 which explained in a general way what the PRIMAGE project consist of and gave a link to the PRIMAGE website (see Annex 1). Previously, the Project was presented in the Annual Spanish Neuroblastoma Group meeting in Valencia and in the Annual European Brain Tumour Group meeting in Brno. In a second time before having direct contact with some of the responsible Paediatric oncologists of those hospitals during the 10th Annual Oncohaematology Paediatric Spanish Society in Jerez de la Frontera, another letter was sent the 23rd of May 2019 with more details about collaboration (see Annex 1). Lately, new contact was made by e-mail in July 2019.
The Spanish hospitals that have been approached are the following (see Figure 2 to locate them in the map):

- H. Niño Jesús (Madrid)

- H. La Paz (Madrid)
- H. Sant Joan de Deu (Barcelona)
- Vall d´Hebron (Barcelona)
- H. Son Espases (Mallorca)
- H. General Universitario of Alicante
- H. Clínico Universitario of Valencia.
- H. Cruces (Bilbao).
- H. Universitario Virgen de las Nieves (Granada)
- H. Universitario Reina Sofía (Córdoba)
- H. Universitario Virgen del Rocío (Sevilla)
- H. Clínico Universitario Virgen de la Arrixaca (Murcia)
- H. Universitario Regional of Málaga
- H. Miguel Servet (Zaragoza)

Figure 3. Spanish potential collaborating hospitals

In order to present PRIMAGE Project and to discuss details about collaboration, two meetings have been set up to date:

- A face to face meeting with H. Niño Jesús and H. La Paz in Madrid the 16th of October 2019.
- A conference call meeting with H. Sant Joan de Déu and H. Vall d´Hebron the 12th of November 2019.

In the same line, we will meet with H. General of Alicante and H. Clínico of Valencia in the next weeks-months and with any other centre that may ask for it.

As clinical and image data are stored and guarded by each hospital, the Ethics Committee of each of the different collaborating centres will have to approve the PRIMAGE project before sharing any data within this research study. Furthermore, a collaboration agreement will be signed between the project coordinator and the new collaborating centre/registry.

Data from patients with Neuroblastoma and DIPG already treated and followed-up will be pseudonymized using the EUPID (European Patient Identity Management) patient identification tool prior transfer to PRIMAGE repositories (see D3.1).

We have given them the documents listed below to prepare and regulate the collaboration between the hospitals and the PRIMAGE Project:

- Data Transfer Agreement for PRIMAGE H2020 Centralized Repository document between La Fe Health Research Institute, QUIBIM S.L and the external Hospital,
- PRIMAGE Project description for External partners,
- Resolution of the AEMPS (see Annex 2),
- HULAFE´s Ethics Committee approval (see Annex 2)
- General document with the explanation of the procedure and advantages of this collaboration.

Specifically, **H. Son Espases** in Mallorca has the Ethics Committee approval already, and as long as we sign the Data Transfer Agreement for PRIMAGE H2020 Centralized Repository document between La Fe Health Research Institute, QUIBIM S.L and them, they will get access to the PRIMAGE Platform to start providing data from NB and DIPG cases treated there since 2002, whenever it is possible.

Other European hospitals:

At a later time, there have been approached other European hospitals by sending them similar letters as referred previously and we are in the process to set up collaboration.
The European hospitals that have been approached are the following:

- Netherlands Cancer Institute (Amsterdam)
- Centro Hospitalar Universitário do Porto
- University Hospital Centre of Coimbra
- Ospedale pediatrico Bambino Gesu (Rome)
- Ospedale pediatrico Gaslini (Genova)
- Institut Claudius Regaud (Toulouse)
- Milan Institute (Milan)
- Great Ormond (London)
- Children´s Grigore Alexandrescu (Bucharest)

With regards to the European hospitals which differ from the Spanish ones, the documents listed above were sent to the following hospitals:

- Ospedale pediatrico Bambino Gesu (Rome)
- Ospedale pediatrico Gaslini (Genova)
- Children´s Grigore Alexandrescu (Bucharest)

Eventually, the referred documents will be sent to the different external hospitals that will collaborate with PRIMAGE Project to be able to start with task 8.2 by June 2020 (M18 of the Project).

Some other documents that are being finished at this time are the PRIMAGE Centralized Repository Implementation manual (QUIBIM) and update of the Data Management Plan for PRIMAGE Centralized Repository.

3.2 Data from European Registries and Databases

Parallelly and in a similar manner than with the hospitals outside the Consortium, it has been sent two letters to the SIOPE DIPG Registry, the 23rd of May 2019 and the 22nd of July 2019 asking for their collaboration with the PRIMAGE Project, as this Registry contains multiple cases of DIPG with clinical,

biological and imaging data and one of its main objectives is to enable collaborative research (see Annex 1). More detailed information about the SIOPE DIPG Registry can be found in D3.1.

Similar to the retrospective (2002 – 2019) data extraction, SIOPEN-r-net will provide NB-based clinical, imaging and biological data out of clinical trials since the HR-NBL1/SIOPEN trial was extended by one year (till October 2020) and new cases will be integrated from 2020 on (see Figure 2). The exact strategy of data extraction and curation is still being worked out.

3.3 Data from Clinical Partners

New diagnosed and treated cases of NB and DIPG in the Clinical Partners (HULAFE, CCRI, UKOELN, UNIPI) from 2020 to 2022 will be incorporated to the PRIMAGE dataset for external validation.
Those patients whose data will be incorporated to PRIMAGE Platform will undergo the standard of care regarding physical interventions for diagnosis and treatments of their diseases as in normal clinical practice (such as imaging, histology, and genetic tests) before entering our registry. There won´t be any intervention on them (see D11.2 for more details).

4. Technical issues

The type of data to be collected for the external validation will follow the same criteria as described in WP3 for the training and internal validation (i.e. clinical, pathological, biological and imaging data). Information systems among hospitals are different between the European countries and also in the same country. It means, data are stored in different ways and formats and information is not structured or easily available. The technical issues regarding the implementation of PRIMAGE database and mechanisms for archiving and storing imaging data, linkable to clinical data will be explained and detailed in D3.2.

5. Conclusion

This document gives an explanation about the readiness to start recruitment for independent data for achieving the dataset to validate externally the PRIMAGE prediction models of tumour behaviour at diagnosis and after the first treatment for NB and DIPG. PRIMAGE Platform will finally act, if proven accurate, as a parallel method enhancing the clinical management of future patients.

It also describes the formal procedures performed to request access to data to the responsible entities (hospitals and registries) for the management of the respective registries and electronic clinical histories.

In addition, this deliverable also presents some achievements committed by the PRIMAGE Project at this point (M12): the favourable dictum of the Ethics Committee Research from the University and Polytechnic Hospital La Fe, the St. Anna Kinderkrebsforschung Children´s Cancer Research Institute (CCRI), the University Hospital of Pisa (UNIPI) and the resolution of the AEMPS (Spanish Agency of Medicine and Health products). The University Clinic of Koeln is pending resolution from its Ethics Committee.

Thus, HULAFE as WP8 leader in collaboration with the other Clinical Partners have begun the means to collect as many independent cases as possible from 2002 to 2022 for the *in silico* external validation.

ANNEX 1: Letters of collaboration

1. First letter to Spanish hospitals:

Hospital Universitario y Politécnico La Fe,
GICT-Cáncer IIS La Fe
Avda. Fernando Abril Martorell 106
46026 Valencia
Teléfono: 34-686933743

Valencia 11 de abril de 2019

Estimados compañeros,

Os escribimos desde el grupo de trabajo Neuroblastoma de la SEHOP para informaros de que el proyecto PRIMAGE (PRedictive In-silico Multiscale Analytics to support cancer personalized diagnosis and prognosis, Empowered by imaging biomarkers), bajo el marco de la financiación europeo Horizonte 2020, ha sido recientemente aprobado por el Comité de Ética en el hospital La Fe y tenemos autorización para iniciar la recogida de casos.

PRIMAGE engloba a un consorcio de 16 instituciones europeas, incluyendo Hospitales, Centros de Investigación y Desarrollo, Asociaciones médicas, Compañías privadas y Universidades, de 8 países diferentes de Europa (España, Alemania, Francia, Austria, Reino Unido, Bélgica, Polonia e Italia). Se trata de un proyecto liderado por el Dr. Luis Martí-Bonmatí, jefe de Departamento de Imagen Médica del Hospital Universitario y Politécnico de La Fe de Valencia, desde el Grupo de Investigación Biomédica en Imagen (GIBI 2^{30}). Además, cuenta con la participación de la SIOPE, el grupo de investigación traslacional en cáncer infantil de La Fe, y otros 2 hospitales europeos referentes en neuroblastoma: el Hospital Universitario de Colonia (Alemania) y el St. Anna Kinderkrebsforschung, CCRI (Austria).

PRIMAGE propone la creación de una plataforma digital abierta para apoyar decisiones en el manejo de dos tipos de cánceres pediátricos: el neuroblastoma (NB) y también el Glioma Difuso de Puente (DIPG). La plataforma incorporará los últimos avances en biomarcadores de imagen *in-silico* y de modelado de crecimiento tumoral para el diagnóstico, pronóstico y seguimiento del tratamiento de forma personalizada, utilizando datos del mundo real (RWD) e integrándolos con los marcadores biológicos que se conocen hasta el momento.

Para ello, se revisarán las historias clínicas y se obtendrán y procesarán las imágenes anonimizadas (RM, TC, MIBG, PET/TC) de los pacientes diagnosticados y tratados de NB y DIPG, desde los registros y centros que colaboran a nivel europeo y nacional. Es en este punto donde queremos pediros colaboración, compartiendo con PRIMAGE los datos e imágenes de vuestros pacientes con tumores neuroblásticos y DIPG. En caso de que decidáis colaborar en este proyecto de I+D, os facilitaremos una memoria de éste donde se indica qué tipo de datos se requieren y cómo serán tratados para que la presentéis a vuestro respectivo Comité de Ética, solicitando el acceso a los datos al proyecto PRIMAGE. Así mismo, necesitaríamos un radiólogo de contacto de vuestro hospital.

La coordinación del proyecto es consciente del esfuerzo extra que representa para clínicos y radiólogos y diseñará una vía para consensuar cómo canalizar una compensación a esa ayuda participando en comunicaciones y trabajos científicos, así como en el acceso a las herramientas que se generen en el proyecto.

Adjuntamos link a la web del proyecto (www.primageproject.eu) y un pdf que ilustra las ideas más claves del mismo.

Esperamos que os parezca una idea tan atractiva como nos parece a nosotros. Os iremos informando de más progresos. Si queréis colaborar podéis contactar con Blanca Martínez (blanca_martinez@iislafe.es) médico pediatra oncóloga responsable de la gestión de la parte de datos clínicos a nivel nacional en el proyecto.

Gracias por vuestra atención y tiempo,

Un saludo a todos.

Dra. Adela Cañete Nieto
J. Sección Oncología Pediátrica

Blanca Martínez de las Heras
Médico Pediatra oncóloga

2. Second letter to Spanish hospitals:

Instituto de Investigación Sanitaria La Fe

Valencia, 23 de mayo de 2019

Estimados compañeros,

Os escribimos en esta segunda ocasión para concretar la colaboración que os pedimos para el proyecto PRIMAGE y detallaros qué tendrías que hacer y qué beneficios obtendríais.

Como sabéis, PRIMAGE creará una plataforma digital abierta para apoyar la toma de decisiones en el manejo de dos tipos de cánceres pediátricos: el neuroblastoma (NB) y también el Glioma Difuso de Puente (DIPG). En esta plataforma, que se está desarrollando actualmente, se incorporarán datos clínicos que consideramos necesarios de los pacientes y se combinarán con datos de las imágenes y sus biomarcadores.

Para subir los datos de los pacientes a la plataforma será necesario que el proyecto sea aceptado por vuestros respectivos Comités Éticos (CEIC). Para ello os facilitamos la memoria del proyecto, el dictamen favorable del CEIC de La Fe y la clasificación como Observacional por la AEMPS). Una vez aprobado se os creará un usuario y contraseña para acceder a la plataforma y así poder comenzar a incluir datos de los pacientes con todas las garantías de protección de datos (LOPD). También necesitamos que nos facilitéis el contacto de un pediatra y un radiólogo que serán los encargados de esta colaboración.

Los pasos serán los siguientes:

1. Acceso a la plataforma con usuario y contraseña desde el hospital.
2. Introducción de datos de pacientes como nuevo sujeto, con anonimización automática.
3. Introducción de datos según pestañas.
4. Incorporación de las imágenes a la plataforma.

De esta forma la plataforma combinará los últimos avances en biomarcadores de imagen *in-silico* y de modelado de crecimiento tumoral a partir de las imágenes con los datos del mundo real (RWD) y los marcadores biológicos que se conocen hasta el momento en la estimación personalizada del fenotipado, seguimiento del tratamiento y pronóstico.

Vuestra colaboración y ayuda estará reflejada, según el grado de participación, en autoría para comunicaciones y trabajos científicos, así como en el acceso a las herramientas que se generen en este proyecto de forma gratuita.

Es necesario firmar el acuerdo de colaboración que os adjuntaremos si nos contestáis positivamente. Cualquier duda por favor contactar con la Dra. Blanca Martínez (blanca_martinez@iislafe.es), pediatra oncóloga responsable de la gestión de datos clínicos en el proyecto.

Gracias de nuevo por vuestra atención y tiempo,

Un saludo a todos.

Dra. Adela Cañete Nieto
Jefa Sección Oncología Pediátrica

Dr. Luis Martí-Bonmatí
Jefe Servicio Radiología

La Fe Health Research Institute
Avenida Fernando Abril Martorell, nº 106, Torre A, 7ª. 46026 Valencia
Tel.: (+34) 96 124 66 01 | Fax. (+34) 96 124 66 20 | info@iislafe.es | www.iislafe.es

3. First letter to SIOPE DIPG Registry

Instituto de Investigación Sanitaria La Fe

Hospital Universitario y Politécnico La Fe,
GICT-Cáncer IIS La Fe
Avda. Fernando Abril Martorell 106
46026 Valencia
Teléfono: 34-686933743

Valencia, 23th May 2019

Dear members of the Executive Committee´s SIOPE DIPG registry,

We are addressing you as leader partners of a European Project on childhood cancer with the proposal of asking for your collaboration.

PRIMAGE (PRedictive In-silico Multiscale Analytics to support cancer personalized diagnosis and prognosis, Empowered by imaging biomarkers), under the European financing framework Horizon 2020, has recently been approved by the Ethics Committee of Hospital Universitario y Politécnico La Fe (Valencia, Spain). Some of you may recall that it was introduced briefly at HGG-meeting in Brno earlier this year by Dr. Cañete.

PRIMAGE includes a consortium from 16 European institutions, including Hospitals, R&D Centres, Medical Associations, Private Companies and Universities from 8 European countries (Spain, Germany, France, Austria, United Kingdom, Belgium, Poland and Italy). This project is led by Dr. Luis Martí-Bonmatí, Chairman of the Medical Imaging Department and Biomedical Imaging Research Group (GIBI230). It counts with the participation of the Clinical and Translational Research in Childhood Cancer of La Fe, and two other main European hospitals which are reference in pediatric oncology: University Hospital of Cologne (Germany) and St. Anna Kinderkrebsforschung-CCRI (Austria).

The project proposes an open cloud-based platform to support decision making in the clinical management of two pediatric cancers, Neuroblastoma (NB), the most frequent solid cancer of early childhood, and the Diffuse Intrinsic Pontine Glioma (DIPG), the leading cause of brain tumor-related death in children. PRIMAGE platform will implement the latest advancement of *in-silico* imaging biomarkers, artificial intelligence and modelling of tumor behavior for the diagnosis, predictive and prognosis follow-up in a personalized way, using data from real world (RWD) practice.

We kindly ask you for collaboration. The data modelling needs a large number of patients to be trained and testing. Sharing patients' data registered in the SIOPE DIPG registry will help the project to achieve expected results on the construction of the clinical decision support system platform. The project is ongoing and financing issues are already set up, but we are willing to discuss practical issues to facilitate this collaboration. This tool will be also available to you.

Please, visit the PRIMAGE website (www.primageproject.eu) for further information. Find attached also a brochure. We are willing to have a conference call to define the collaboration. We fully keep at your disposal. Looking forward to your comments.

Thank you very much in advance.

Yours sincerely,

Dra. Adela Cañete Nieto
Chief of Pediatric Oncology Unit

Dr. Luis Martí-Bonmatí
Director Medical Imaging Department Valencia

La Fe Health Research Institute
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4. Second letter to SIOPE DIPG Registry

Instituto de Investigación Sanitaria La Fe

Valencia, 22nd July 2019

Hospital Universitario y Politécnico La Fe,
GICT-Cáncer IIS La Fe
Avda. Fernando Abril Martorell 106
46026 Valencia
Phone: +34-686933743

Dear members of the Executive Committee´s SIOPE DIPG Registry, dear Sophie,

We are addressing you to detail our proposal for collaboration within the PRIMAGE Project.

PRIMAGE will create an open digital platform to support decision making in the management of two types of pediatric cancers: Neuroblastoma and Diffuse Intrinsic Pontine Glioma. In this platform, which is currently being developed under an H2020 programme, clinical-molecular-imaging data will be incorporated and integrated as phenotyping-predicting-prognosis biomarkers.

As data modelling requires a large number of patients for the training and testing, sharing your DIPG patients' data will help the project to achieve the expected results on the construction of the clinical decision support platform.

If you agree, although the project financing issues are already set up and closed, our mutual collaboration can be reflected in PRIMAGE recognition, invitations to PRIMAGE meetings, access to PRIMAGE data and results, authorship for scientific papers and meetings, open access to the developed decision support tools and opportunities for next joint actions and proposals.

Please, visit the PRIMAGE website (www.primageproject.eu) for further information and find also attached a brochure. We can schedule a conference call to further define the collaboration.

Keeping at your disposal and looking forward to your comments.

Thank you very much in advance.

Yours sincerely,

Dra. Adela Cañete Nieto
Chief of Pediatric Oncology Unit

Dr. Luis Martí-Bonmatí
Director Medical Imaging Department

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ANNEX 2: AEMPS resolution

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

S 201901700000476
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
Puede comprobar la autenticidad del documento en la sede de la AEMPS: https://sede.aemps.gob.es

Localizador: RG3L61E28F

Página 1 de 3

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28022 MADRID

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

agencia española de medicamentos y productos sanitarios

DEPARTAMENTO DE MEDICAMENTOS DE USO HUMANO

ASUNTO: **RESOLUCIÓN DEL PROCEDIMIENTO DE CLASIFICACIÓN DE ESTUDIO CLÍNICO O EPIDEMIOLÓGICO**

DESTINATARIO: **Dª VANESSA SEGURA CABALLER**

Vista la solicitud-propuesta formulada con fecha **11 de marzo de 2019**, por **Dª VANESSA SEGURA CABALLER,** para la clasificación del estudio titulado **"PRedictive In-silico Multiscale Analytics to support cancer personalized diaGnosis and prognosis, Empowered by imaging biomarkers"**, y cuyo promotor es **Luis Martí Bonmatí,** se emite resolución.

El Departamento de Medicamentos de Uso Humano de la Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), de conformidad con los preceptos aplicables, (1) **RESUELVE** clasificar el estudio citado anteriormente como "**Estudio *Observacional No Posautorización***" (abreviado como No-EPA).

Para el inicio del estudio no se requiere la autorización previa de ninguna autoridad competente (AEMPS o CCAA) (2), pero sí es necesario presentarlo a un CEIC acreditado en nuestro país y obtener su dictamen favorable.

El promotor tendrá que informar a los responsables de las entidades proveedoras de servicios sanitarios donde se lleve a cabo el estudio y les entregará copia del protocolo y de los documentos que acrediten la aprobación por parte del CEIC y, en su caso, la clasificación de la AEMPS. Asimismo estos documentos se entregarán a los órganos competentes de las CC.AA., cuando sea requerido. La gestión y formalización del contrato estará sujeta a los requisitos específicos de cada Comunidad Autónoma.

C/ CAMPEZO, 1 - EDIFICIO 8
28022 MADRID

MINISTERIO DE SANIDAD, CONSUMO Y BIENESTAR SOCIAL

agencia española de medicamentos y productos sanitarios

DEPARTAMENTO
DE MEDICAMENTOS
DE USO HUMANO

Contra la presente resolución que pone fin a la vía administrativa podrá interponerse Recurso Potestativo de Reposición, ante la Directora de la Agencia, en el plazo de un mes a contar desde el día siguiente a aquel en que tenga lugar la notificación de la presente resolución. (3)

Madrid, a 12 de marzo de 2019
JEFE DE DEPARTAMENTO DE MEDICAMENTOS DE USO HUMANO

agencia española de medicamentos y productos sanitarios

Fdo. Cesar Hernández García

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[1] Son de aplicación al presente procedimiento la Ley 39/2015, de 1 de octubre, del Procedimiento Administrativo Común de las Administraciones Públicas; la Ley 14/2000, de 29 de diciembre, de medidas fiscales, administrativas y de orden social; Real Decreto Legislativo 1/2015, de 24 de julio, por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios; Real Decreto 1090/2015, de 4 de diciembre, por el que se regulan los ensayos clínicos con medicamentos, los Comités de Ética de la Investigación con medicamentos y el Registro Español de Estudios Clínicos; el Real Decreto 1275/2011, de 16 de septiembre, por el que se crea la Agencia estatal "Agencia Española de Medicamentos y Productos Sanitarios" y se aprueba su estatuto; el Real Decreto 577/2013, de 26 de julio, por el que se regula la farmacovigilancia de medicamentos de uso humano y la Orden SAS/3470/2009, de 16 de diciembre, por la que se publican las directrices sobre estudios posautorización de tipo observacional para medicamentos de uso humano.

[2] De acuerdo con la Orden SAS/3470/2009, de 16 de diciembre

[3] De conformidad con lo dispuesto en la Ley 39/2015, de 1 de octubre, o Recurso Contencioso-Administrativo ante el Juzgado Central de lo Contencioso-Administrativo de Madrid, en el plazo de dos meses contados desde el día siguiente al de la notificación de la presente resolución, de conformidad con la Ley 29/1998, de 13 de Julio, reguladora de la Jurisdicción Contencioso-Administrativa, sin perjuicio de poder ejercitar cualquier otro recurso que se estime oportuno. En caso de interponerse recurso de reposición no podrá interponerse recurso contencioso-administrativo hasta la resolución expresa o presunta del primero.

Agencia Española de Medicamentos y Productos Sanitarios
Fecha de la firma: 12/03/2019
Puede comprobar la autenticidad del documento en la sede de la AEMPS: https://sede.aemps.gob.es
Localizador: RG3L69E28F

Página 3 de 3

C/ CAMPEZO, 1 - EDIFICIO 8
28022 MADRID

ANNEX 3: Ethics Committee approvals

1. HULAFE Ethics Committee approval:

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,**

CERTIFICA

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

2. CCRI Ethics Committee approval:

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:

Seite 2/3

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/

3. UNIPI Ethics Committee approval

Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana
Sezione: COMITATO ETICO PEDIATRICO
Segreteria Tecnico Scientifica ubicata c/o: Meyer - Viale Pieraccini, 28 - 50139 Firenze
Telefono: 055-5662386 E-mail: comitato.etico@meyer.it

Firenze, il... 30/09/2019
Pag. 2 con la presente

Al promotore Ospedale Universitario Politecnico di La Fe

Allo sperimentatore principale Prof. Emanuele Neri
Sezione Dipartimentale Radiodiagnostica 3 - AOUPisana

Oggetto: Comunicazione del parere relativo alla richiesta di approvazione alla conduzione dello studio clinico dal titolo *PRedictive In-silico Multiscale Analytics to support cancer personalized diaGnosis and prognosis, Empowered by imaging biomarkers business place (PRIMAGE)*
Codice Protocollo: PRIMAGE

In riferimento alla richiesta di cui all'oggetto, si trasmette il parere del Comitato Etico Regionale per la Sperimentazione Clinica della Toscana - sezione COMITATO ETICO PEDIATRICO riunitosi in data **24/09/2019**.

Si ricorda che l'avvio della sperimentazione da parte del Promotore è subordinato al rilascio della disposizione autorizzativa della Direzione Generale dell'Azienda sanitaria.
Il Comitato si riserva la facoltà di monitorare nel corso del suo svolgimento, in accordo alle disposizioni normative vigenti, lo studio clinico approvato.

Il Responsabile Segreteria Tecnico Scientifica

Segreteria Scientifica del Comitato Etico Pediatrico
Sezione Autonoma del Comitato Etico Regionale
per la Sperimentazione Clinica
c/o Azienda Ospedaliero Universitaria Meyer
Viale Pieraccini, 24 - 50139 FIRENZE

Il Comitato Etico in osservanza alle legislazioni vigenti in materia di studi osservazionali
ha esaminato la richiesta di parere relativa allo studio in oggetto

Avendo valutato la seguente documentazione:

- ✓ Sintesi del protocollo in lingua italiana (versione 1 del 22/07/2019)
- ✓ Dichiarazione sulla natura osservazionale dello studio (versione -- del 01/08/2019)
- ✓ Protocollo di studio (versione 1 del 22/07/2019)
- ✓ Parere Unico del Centro Coordinatore (se applicabile) (versione -- del 27/03/2019)
- ✓ Elenco dei Centri partecipanti (se multicentrico) (versione 1 del 22/07/2019)
- ✓ Scheda di raccolta dati (versione 1 del 22/07/2019)
- ✓ Certificato marchio CE del dispositivo medico (versione -- del 11/01/2019)
- ✓ Scheda tecnica del dispositivo medico
- ✓ Scheda tecnico legale del dispositivo medico

- ✓ Manuale dispositivo
- ✓ Dichiarazione per l'accertamento della natura indipendente dello studio (versione -- del 01/08/2019)
- ✓ Lettera di intenti del promotore per il CE (versione - del 01/08/2019)
- ✓ Lettera di accettazione dello sperimentatore locale (versione - del 01/08/2019)
- ✓ Analisi d'impatto aziendale per la fattibilità locale (versione - del 01/08/2019)
- ✓ Curriculum vitae in formato UE aggiornato dello sperimentatore locale (versione - del 05/08/2019)
- ✓ Dichiarazione pubblica sul conflitto di interessi (versione - del 01/08/2019)
- ✓ Dichiarazione natura indipendente e no profit dello studio (versione - del 01/08/2019)
- ✓ Dichiarazione natura osservazionale (versione - del 01/08/2019)
- ✓ Medical Devide (DM) per indagini cliniche in valutazione B7 (versione - del 01/08/2019)
- ✓ Analisi impatto aziendale firmata dal DS (versione - del 06/09/2019)
- ✓ Foglio Informativo e consenso per genitori/tutore legale (versione – del 04/07/2019)
- ✓ Foglio Informativo e assenso per pazienti 14-18 anni (versione – del 22/07/2019)
- ✓ Foglio Informativo e assenso per pazienti 7-13 anni (versione – del 22/07/2019)

Ha espresso:
PARERE FAVOREVOLE

Numero registro pareri del Comitato Etico: 173/2019

Elenco componenti del CE presenti alla discussione e votanti che hanno dichiarato assenza di conflitti di interessi di tipo diretto o indiretto:
Prof. Alessandro Mugelli, *Farmacologo*
Dr.ssa Maria Bimbi, *Medico Medicina Generale*
Dr. Antonio Ciccarone, *Fisico area radiologica*
Dr.ssa Paola Cipriani, *Clinico neuropsichiatra infantile*
Dr.ssa Maria Grazia Conti, *Pediatra di famiglia*
Dr. Emanuele Crocetti, *Biostatistico*
Dr.ssa Lorena Di Simone, *Farmacista del SSR*
Prof. Giovanni Marello, *Medico legale*
Dr. Eugenio Paci, *Esperto clinico settore procedure diagnostiche e terapeutiche*
Dr.ssa Silvia Paoli, *Rappr. area professioni sanitarie interessate alla sperimentazione*
Prof.ssa Monica Toraldo di Francia, *Esperto di bioetica*

Elenco componenti del CE presenti non votanti:
Sussistenza numero legale (n. 11 su 20)

Si ricorda che è obbligo notificare al Comitato Etico: data di arruolamento del primo paziente e stato di avanzamento dello studio, con cadenza semestrale e/o annuale, corredato da una relazione scritta; fine del periodo di arruolamento; data di conclusione dello studio a livello locale ed a livello globale e risultati dello studio, entro un anno dalla conclusione della stessa. Inoltre si ricorda di riferire immediatamente al Comitato: deviazioni dal protocollo, modifiche al protocollo.

Comitato Etico Pediatrico
SEZIONE AUTONOMA DEL COMITATO ETICO REGIONALE
PER LA SPERIMENTAZIONE CLINICA
c/o AZIENDA OSPEDALIERO UNIVERSITARIA MEYER
Viale Pieraccini, 24 - 50139 FIRENZE

Il Presidente