BD2Decide

Big Data and models for personalized Head and Neck Cancer Decision support

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This document should be distributed as guidance to all the personnel of BD2Decide Consortium partners involved in the project execution.

Revision History

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1	28.11.2016	E. Martinelli (AOP)	ToC and first contribution by AOP
1.1	01.12.2016	S. Canevari (INT)	Contribution to ethics for genomics
2	15.12.2016	V. Tountopoulos (ATC)	Contributions to sections 4.2 and 4.3
2.1	15.12.2016	A. Fioravanti (UPM), F. Jung (Fraunhofer), M. Silva (UNIPR), G. Arcuri (AOP)	Contributions to section 4 concerning ethics for diagnotic images management
3	20.12.2016	L. De Cecco (INT), R. Brakenhoff (VUmc), K. Scheckenbach (UDUS)	Contribution to ethics on genomics and genomics data management
3.1	23.12.2016	K. Scheckenback (UDUS)	Semi-final version
4	30.12.2016	E.Martinelli (AOP)	Final version

Addressees of this document

This document is addressed to the BD2Decide Consortium. It is intended to guide BD2Decide investigators conducting BD2Decide study, including audits and related activities.

It describes the actions in place to meet ethics requirements in BD2Decide.

The document is delivered to the European Commission as defined in DoA.

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Abbreviations and definitions

BAM	Binary Alignment Map
CRF	Case Report Form
DNA	Desoxyribonucleic Acid
DoA	Description of Action
DTA	Data Transfer Agreement
EC	European Community
FFPE	Formalin fixed Paraffin-embeded
HPV	Human Papilloma Virus
ICF	Informed Consent Form
IMRT	Intensity-modulated Radio Therapy
MRI	Magnet Resonance Imaging
MTA	Material Transfer Agreement
OECD	Organisation for Economic Co-operation and Development
PI	Principal Investigator
Pseudonynìmization	Pseudonymization techniques (e.g. encoding) allows the local centers to refer the patients' data to the patients and is therefore useful/necessary for a correct follow up while external persons/partners cannot identify the patient.
SOP	Standard Operating Procedure
RNA	Ribonucleic Acid
RT	Radio therapy
SOP	Standard Operating Procedure: detailed written instructions for the execution of activities in clinical trials
UNESCO	United Nations Educational, Scientific and Cultural Organization
WHO	World Health Organization
WP	Work Package

EXECUTIVE SUMMARY

BD2Decide Ethics framework has set rules to manage personal data, diagnostic images and biologic samples of the BD2Decide clinical study subjects. These rules have informed the actions implemented by the Consortium to guarantee that the privacy, dignity and health of patients participating to the clinical study are safeguarded. These actions address the following aspects:

1) Ensure health of patients: the BD2Decide study is an observational study and as such no modifications to the best practices in head and neck cancer diagnosis and treatment are nor will be performed. The Ethics Committees of all participating hospitals have approved the BD2Decide study protocol. Copies of the approval documents have been collected by the Coordinator.

2) Achieve informed consent by patients: all BD2Decide patients have provided and signed / will be asked to sign an informed consent form. The PIs of each participating hospital are bound to present and describe in details the clinical study to the patient before acquiring their informed consent. The consent may be withdrawn anytime.

3) Acquire consent for retrospective patients. For the hospitals in Germany (UDUS and subcontractor ULM) and in The Netherlands a general informed consent is provided and signed by patients: this consent has been acquired and is available at the Coordinators' premises as well. In Italy INT and AOP have obtained informed consent for all retrospective patients still alive and who could be reached, as foreseen by Italian regulations concerning clinical studies.

4) Manage patient consent: the PIs of participating hospitals have set a procedure, according to the protocol approved by Ethics Committees, to deal with patient's withdrawal. A Data Transfer Agreement (DTA) and a Materials Transfer Agreement (MTA) are currently being signed by Consortium partners which regulate the destruction of all data and biologic specimens of patients withdrawing from BD2Decide before the end of the study.

5) Guarantee privacy: non-disclosure of patients' identity is managed
   a. patients' data and diagnostic images are encoded before being shared outside the hospital in charge of patients' care;
   b. all information (e.g. place of birth, address, phone etc.) that might disclose the patient's identity is not used by BD2Decide;
   c. ethnicity, religion, sexual habits or other potentially discriminating factors are removed from the shared patients' data;
   d. diagnostic images are pseudonymized before being processed by the Image Analysis Tools developed by Fraunhofer;
   e. RNAseq will not include either germline whole genome or germline whole exome DNA sequencing, thus, we will not recover any data about SNPs or INDELs able to identify patients. BAM files will be processed by INT in a separated server and only gene expression processed data that do not contain any data on nucleotide sequencing (raw data) will be shared. BAM files will be manually (not via network channels) transferred

to the owing hospital and then deleted from INT server immediately after the generation of raw data files;

6) manage patients' data and biological materials sharing: the DTA and the MTA (see except in annex) between BD2Decide partners regulate the management of shared pseudonymized/encoded data and biologic specimens, that will be destroyed in case of patient's withdrawal and at the end of the BD2Decide project;

7) ensure data integrity, security and recovery: data encryption, backup procedures have been set by the Consortium;

8) ensure data consistency: verification vs. original patients' health records is guaranteed by the PIs of each participating hospital, who signs and approves the data stored into BD2Decide repositories;

9) disclosure of incidental findings to patients: each PI will manage incidental findings according to the ethical rules of the relevant hospital; in general terms, as described in section 5 of the DoA, incidental findings having consequences on patient's health will be communicated to the patient by the relevant PI.

ABOUT THIS DOCUMENT

This document describes the actions applied to the BD2Decide project to guarantee compliance to all Ethics aspects concerned with the project execution and the management of the clinical study,

It contains:

- A summary of the application scope.
- The definition of the Ethics Framework for the project.
- The details of all ethics aspects addressed and the implemented monitoring activities.
- The main roles (persons, organizations and bodies) that overview on ethics.
- The description of the mechanisms applied to ensure ethics management.
- The description of the mechanisms to ensure effective management in case of breach of ethics.

Appendixes provide the following reference material:

- Ethics approvals by Ethics Committees of participating centres.
- Templates of the Informed Consent forms signed by patients enrolled for the BD2Decide clinical study.
- References to important documents.

1 PRINCIPLES AND OBJECTIVES

1.1 SCOPE

Ethics aspects in BD2Decide relate to the execution of the clinical study and to the assessment of clinical impacts as defined in the Technical Annex I - DoA, section 5 Ethics.

The main ethical aspects addressed and monitored throughout the project concern the following:

1. Comply with all Human Rights during the project execution, for patients and for BD2DecideConsortium members.
2. Ensure the best and most appropriate treatment to patients involved in BD2Decide clinical study, in order to preserve and enhance their health as much as possible, in compliance with best clinical practice.
3. Guarantee patients' right to privacy, ethical management of their data and biologic specimen, in conformity with EU and national laws and regulations and in compliance to the informed consent signed by each patient entering the study.
4. Prevent undue disclosure of data to un-authorized persons.
5. Guarantee data security and recovery.
6. Regulate access, use and disposal of personal data and biological samples used for the clinical study execution.
7. Ensure non-disclosure of individual patient's information in publications and in any dissemination actions performed in the frame of the project.
8. Regulate the extraction and management of genomic and radiomics data extracted from biologic specimen and diagnostic images respectively, in order to prevent the identification of individuals; set rules for data coding and pseudonymization.
9. Set rules that guarantee all the above mentioned points 1 to 8 after the end of the project.
10. Guarantee that no discriminations are applied concerning, gender. ethnicity, religion or any other condition except the health conditions required to enter the clinical study (see Clinical Study protocol approved by Ethics Committee) to both patients and BD2Decide Consortium staff.
11. Ensure that the clinical study protocol - and its modification should any occur during the study execution - are approved by Ethics Committees of all participating clinics.
12. Verify that the clinical study is published on clinical trials registry.

All these actions have been addressed by the Ethics Manager and by all Consortium members and are detailed in this document.

The legal basis for our Ethics framework is detailed in the Technical Annex I - DoA, section 5 "Ethics" and in deliverables D10.1, D10.2, D10.3 , Quality Management procedures established in D1.1 and Material and Data Transfer Agreements under signature by BD2Decide Consortium.

1.2 THE ETHICS CONTEXT OF BD2DECIDE

BD2Decide is an observational study, i.e. manages patients enrolled retrospectively and prospectively, and data obtained without any additional therapy or monitoring procedure. As such BD2Decide study is relatively low-risk for two reasons: the investigators observe and analyze information about the health (and disease outcome) of the patients, but do not alter the care or treatment administered and secondly there is a minimum potential for conflict between the investigator role and the clinician role.

Universal principles, such as the Helsinki Declaration and the general privacy and patient's health preservation regulations apply. Ethics approval to the detailed study protocol is prerequisite to the start of the study.

However, the modalities of the application of ethics regulations vary from one country to another. To avoid potential problems for the conduct of BD2Decide multi-centric international study, as well as for the publication of results as the authors and editors come from countries governed by different regulations, an Ethics framework and specific agreements have been established between BD2Decide Consortium partners.

The BD2Decide Ethics is inspired by the recommendations (Twelve Golden Rules for Ethical Research Conduct) published by the European Commission[2]: "Ethics for Researchers".

Besides the approval by Ethics Committees of all participating hospitals, we have ensured the following ethics principles:

- **Respect for patients**: conform to patients will and autonomy in decision to participate through informed consent.
- **Justice**: avoid imposing on particular groups an unfair burden of participation in research, fair inclusion and exclusion conditions for participants, no discrimination in the selection and recruitment of participants.
- **Beneficence and non-maleficence**: BD2Decide study does not modify the best clinical practices for Head and Neck cancer patients treatment, but increases the clinicians' knowledge and insight on patient's individual disease presentation.
- **Integrity:** PIs engaged in the advancement of knowledge expected from BD2Decide are bound to conduct honest and thoughtful inquiry and rigorous analysis, and are accountable for their activities.
- **Diversity**: PIs must take into consideration the needs, values, and beliefs of each individual patient. In this sense we have designed the informed consent and envisaged the Patients co-decision aid.
- **Conflict of interest**: no conflict of interest exist as BD2Decide is not industry sponsored and is an observational study.

[2] See: http://ec.europa.eu/research/participants/data/ref/fp7/89888/ethics-for-researchers_en.pdf

2 ETHICS AND CLINICAL STUDY

BD2Decide foresees a clinical study involving humans, biologic materials, diagnostic images with a critical privacy aspect (CT and MRI scans of the patients' head) and patients' sensitive data. It is important to mention that during the BD2Decide study, the patient´s course of illness is not altered by the study. Materials, imaging and clinical data are collected after (for retrospective cases) or during (for prospective cases) the normal patient´s courses and treatments. Thus ethical aspects have been addressed in depth both in the DoA part B section 5 and in the clinical protocol D7.1.

Regarding Ethical aspects, the Coordinator is responsible to ensure that all participating hospitals fulfill the National and European regulations regarding safety, security, privacy and all aspects concerning the management of the biological specimen and patients data collected during the project. For this scope the Coordinator has requested that all participating hospitals provide the approval of BD2Decide study by their reference Ethical Committees. Copies of the approvals documents are maintained by the Coordinator.

Ethical Committees established in each clinical centre have approved the clinical study protocols (for prospective study and for retrospective study) and the relevant ethics framework and quality assurance guidelines have been set as part of the protocol.

Investigators conducting, or involved in conducting, observational studies are responsible for ensuring these studies meet ethical standards. When there is more than one investigator, the principal investigators (dr. Lisa Licitra and dr. Tito Poli) have the overall responsibility for the ethics of the activity. An Ethics Manager (Dr. Kathrin Scheckenbach, UDUS) has been appointed to support the PIs..

The greater the risk of harm from an observational study, the greater the care that is required in assessing and addressing the ethical issues raised.

Failure to satisfy an ethics requirement is an extremely serious non-conformity that can stop the clinical study execution and consequently invalidate or jeopardize the project execution and results. Therefore, it should be immediately addressed through adequate corrective and preventive actions and should also be monitored as part of risk management.

2.1 GENERAL FRAMEWORK

As already described in BD2Decide DoA section 5, the general foundations of our Ethical Policy is the Charter of Fundamental Rights of the European Union (in particular art. 35 stating the right to medical treatment and preventive healthcare). The Consortium will manage ethical aspects according to the following rules and principles.

- The Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and the relevant national derivative regulations;
- The Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (art I.3 and I.4 related to the careful assessment of risks to the subject), and all

articles of section III. Non-therapeutic clinical research, related to the obligation for patients' informed consent and right to withdraw as well as to the safeguard of patient's dignity and personal integrity.

- The Data Protection Act (1988) and Data Protection Amendment (2003), Directive 2002/58/EC on Privacy and Electronic Communications (amending Directive 97/66/EC), regulating personal information protection across the telecommunications sector;
- The Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research (CETS No. 195, 2005), reaffirming the fundamental principle for research involving human beings: free, informed, express, specific, and documented consent of the person(s) participating.

2.1.1 Collection and management of biologic samples

For the BD2Decide study materials and samples are used that are routinely collected and processed during patient´s treatment. Thus ethical and legal frameworks for this aspect are already in place in all participating hospitals, as required by National and EU regulations.

- The Universal Declaration on the Human Genome and Human Rights, UNESCO Gen. Conf. Res. 29 C/Res.16, reprinted in Records of the General Conference, UNESCO, 29th Sess., 29 C/Resolution 19, at 41 (1997) (adopted by the UN General Assembly, G.A. res. 152, U.N. GAOR, 53rd Sess., U.N. Doc. A/RES/53/152 (1999), especially art. 5, 7 and 9 regarding informed consent, protection and confidentiality of genetic data.
- The Opinion of the European Group of Ethics in science and new technologies to the E.C. Ethical aspects of human tissue banking providing definitions for human tissues and of tissues management procedures and guidance regarding tissues donation information and consent.
- The principles of Protection of the human genome by the Council of Europe (Doc. 9002 - March 2001), stating the protection and respect of the human genome and its basic component, in order to prevent unethical and unlawful utilization for profitable reasons.
- The Recommendations of the European Society of Human Genetics regarding Data storage and DNA banking for biomedical research, which addresses technical, social and ethical issues, guidance regarding the usage of already stored anonymous biological samples, obligation to anonymization and data protection and informed consent. The recommendations also set provisions regarding the management, control and security issues related to biologic samples preservation, with special regard to confidentiality.
- The 2009 OECD Guidelines on Human Biobanks and Genetic Research Databases providing guidance for the establishment, governance, management, operation, access, use and discontinuation of human bio-banks and genetic research databases.
- The Recommendation Rec(2006)4 of the Committee of Ministers to member states on research on biological materials of human origin, which sets obligations regarding the collection, consent to usage and withdrawal option, obligations for identifiable biologic

materials, to secure confidentiality, privacy, independent decision and safeguard of individuals whose biologic materials are retained for research purposes.

- The ICH guideline E18 on genomic sampling and management of genomic data issued by the European Medicines Agency.

2.2 BD2DECIDE CLINICAL STUDY CONTEXT

The BD2Decide study foresees the collection of retrospective and prospective patients' data and the data extraction from diagnostic images and from genomic and pathology tests on patients biological samples. The objective of the clinical study is to collect existing prognostic models for Head and Neck Cancer, collect multiscale patients' data, analyze them using models and Big Data analysis techniques, and identify prognostic signatures and refined models that can foresee - at the time of diagnosis - the probable disease outcome for each patient and stratify patients by probability of survival (Figure 2-1).

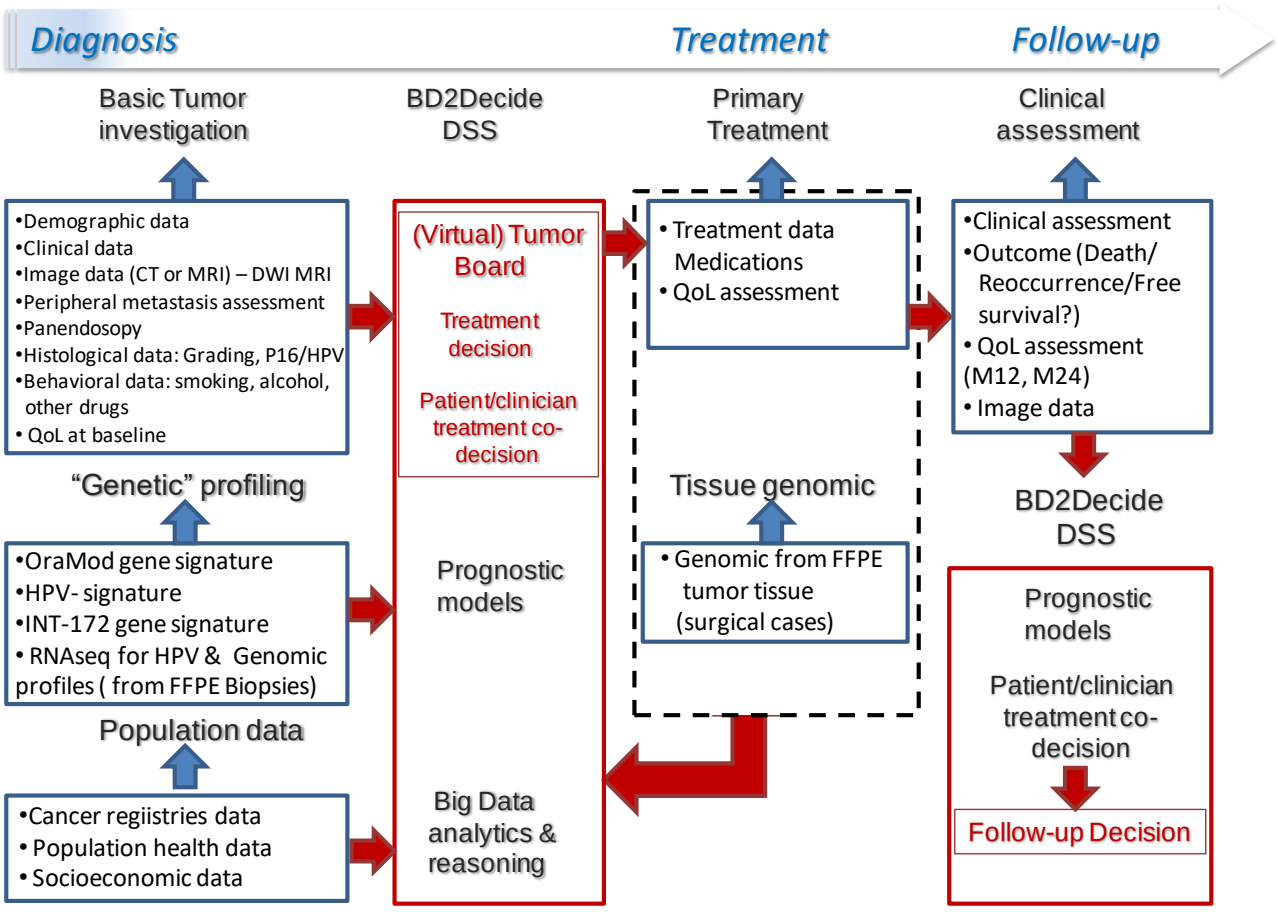

Figure 2-1. Scheme of BD2Decide clinical study

The BD2Decide clinical study is multicentric across 5 EU Countries: Italy, Germany, The Netherlands (AOP, INT, UDUS, VUmc, MAASTRO, Consortium partners; ULM subcontractor), Poland and Portugal (INT subcontractors). All the hospitals have shared a common study protocol and will provide data and biologic specimens. Technology partners (UPM, ATC. AII, Fraunhofer,

VUmc statisticians, MAASTRO radiomics scientists) will access pseudonymized data and analyze them.

The study relies on two patients' cohorts:

1. retrospective cohort: patients enrolled between year 2008 and 2014, whose data are used to re-calibrate the prognostic models and to train and test the Big Data analysis algorithms;
2. prospective cohort: patients enrolled starting 01/01/2015, whose data are used to validate the prognostic models and the Big Data analysis algorithms.

In the frame of this main study, BD2Decide partners are responsible of the following activities:

1. collect patients' data from usual routine in a e-CRF dataset (retrospective data) and in an electronic health record system (prospective patients): all participating hospitals,
2. collect patients' diagnostic images (CT and MRI scans) for features extraction (anatomic and radiomic): all participating hospitals,
3. collect patients biological samples (biopsies, tumor specimens from surgery) and analyze them for pathological and genomic biomarkers: all participating hospitals,
4. share these data among Consortium partners, after pseudonymization, for data analysis: all participating hospitals under MTA and DTA,
5. perform anatomic image features extraction: participating hospitals by means of Fraunhofer image analysis software,
6. perform radiomics signatures extraction from CT scans: MAASTRO researchers using Oncoradiomics software,
7. perform radiomics signatures extraction from MRI and DWI-MRI scans: POLIMI researchers using BD2Decide radiomics software,
8. perform RNAsequencing for gene signatures extraction and HPV status assessment: INT,
9. store and manage data collected in e-CRF: ATC using OpenClinica tool;
10. store and manage patients' data, including BAM files from RNAsequencing, imaging and radiomics data: each participating hospital,
11. manage all patients' data for analysis: AII on a shared repository for Big Data analysis and models execution.

We have therefore considered the following ethical aspects:

1. Informed consent.
2. Data protection and privacy for:
    a. clinical data routinely collected,
    b. diagnostic images and related features extracted by BD2Decide tools (image analysis and radiomics),
    c. genomic data extracted by INT through RNA sequencing techniques.
3. Approval by Ethics Committees.
4. Management of data and biologic specimens during the project (MTA, DTA) and after the end of the project.

5. Maintenance of data used for publications.

The BD2Decide clinical study has been registered by the Coordinator (Ref.: https://clinicaltrials.gov/show/NCT02832102), in compliance with clinical trials standards and to ensure future publications in high-impact journals.

2.3 STUDY PARTICIPANTS INCLUSION

The clinical study protocol sets the criteria for retrospective and prospective patients' enrolment. We have designed the clinical study in adherence with the principles outlined in section 1.2, in particular considering gender aspects.

The following inclusion and exclusion criteria are defined:

INCLUSION CRITERIA
• Provision of subject informed consent (or consent from next of kin/legal representative if applicable) for use of the data and retrieval of tumor sample (where available), or waiver for informed consent according to local national regulations • Histologically confirmed primary diagnosis of oral cavity, oropharynx, larynx, hypopharynx squamous cell carcinoma treated between 2008-2014 (retrospective patients) or at time of recruitment for the study (prospective data) • Clinical stage III and IV (a,b) (c excluded) • Patient candidate for curative treatment: ± surgery ± 3D or intensity modulated RT (IMRT) ± chemotherapy • Adequate archival pre-treatment tumor specimen available (FFPE macrodissected sections) • Availability of baseline CT scan of the head and neck region performed with contiguous cuts of 2-3 mm or less in slice thickness with i.v. contrast or MRI scans with T1 (non or pre-constrast) and T2 acquisitions (slice thickness lower than 3 mm). If both available CT scan is preferred • Male or female ≥ 18 years old.
EXCLUSION CRITERIA
• Any previous head and neck cancer. • Patients with previous malignancies in the last 5 years before treatment for head and neck cancer, with the exception of surgically cured carcinoma in situ of the cervix, in situ breast cancer, incidental finding of stage T1a or T1b prostate cancer, and basal/squamous cell carcinoma of the skin. • Any previous malignancy that was treated with surgery and/or radiation of the head and neck region. Histological type other than head and neck squamous cell cancer (nasopharynx, salivary glands and sinus nasal cancer are excluded).

Table 2-1. BD2Decide study inclusion and exclusion criteria

These criteria do not conflict with ethical issues concerning discrimination of subjects based on gender, ethnicity, religion or other discriminations apart the fulfillment of health conditions relevant for the clinical study execution. No payments or other induced benefits are given to participating

patients to avoid a conflict of interest in this respect. Only patients that are competent of agreement and who are able to understand the study´s finality and their role in the research and clinical study are actively involved. Patients are informed by a medical doctor who is familiar with the study. They are able to post questions at any time. In case of the patient´s wish to withdraw his consent, this is possible at any timepoint without mentioning any reason for this. The patient will therefore receive equal treatment, he will not receive any disprofit. These criteria are mandatory for prospective patients.

If a patient is not able to read, a reliable, independent witness, who is not affiliated with the institution or engaged in the investigation, is defined and present during the entire informed consent discussion. As already described in section 5.2.6 of the BD2Decide DoA, after the patient or legally acceptable representative orally consents and has signed, if capable, the witness should sign and personally date the consent form attesting that the information is accurate and that the patient or legally acceptable representative has fully understood the content of the informed consent agreement and is giving true informed consent.

Within this study, a very high number of retrospective patient´s cases are analyzed to get reasonable data for the aimed model, which is also a prerequisite for the prospective analysis. Therefore, it would be disproportionate to retrospectively receive informed consent of all these retrospective patient´s. Furthermore, within an oncologic study, referring to a patient´s group with a high illness-related morbidity, only including surviving retrospective patients would lead to a bias and a blurred study outcome. Thus, in some centers (UDUS, VUmc, MAASTRO) the ethics committees agreed to include these patient´s data in a strictly pseudoymized way. Any back network is not possible.

Data transfer is regulated be a collectively agreed Data Transfer Agreement and an associated Data Transfer form (in Annex to this document).

2.3.1 Responsibilities and verification procedures

The PIs at each participating centre are responsible to ensure that no discrimination is applied.

After verbal and written explanation of the study, the signature of informed consent as the adequate documentation of this by study participants and the informing doctor is a prerequisite to participation and patients' data and biologic specimen usage for BD2Decide. Only biologic specimen that are anyway taken away during routine surgery and/or biopsy are used. Only specimen, that are not needed for diagnostics any more are integrated into the study.

The e-CRF includes a mandatory declaration of the PI concerning signature of informed consent.

2.4 STUDY APPROVAL BY ETHICS COMMITTEES

The Coordinator has already acquired the approvals by the Ethics Committees of INT, AOP, and UDUS. VUMC and MAASTRO have already achieved Ethics approval for BD2Decide prospective study. The prospective study protocol was submitted first by the leading PI (Lisa Licitra) to the Ethics Committee at INT, and, after approval, was submitted and approved by all other hospitals participating to the clinical study. Two separate protocols have been submitted for the retrospective

and for the prospective study respectively. This decision was taken to cope with institutions such as VUmc that will only participate to the retrospective study and others (such as ULM or INT subcontractors) that will participate to prospective study only.

INT and AOP have achieved informed consent from retrospective patients still alive and have achieved permission by Ethics Committees to extend informed consent given for previous studies in case of dead patients or patients who cannot be reached for a new consent signature.

VUmc and MAASTRO have achieved extended Ethics Approvals for previous studies concerning Head and Neck Cancer Patients, which cover BD2Decide retrospective patients' data collection. UDUS also has an extended Ethical approval on which the BD2-Decide ethical approval is referred to.

Ethics approvals for BD2Decide prospective study in subcontracting hospitals are ongoing. The leading clinics for subcontracted hospitals are responsible for controlling their ethical approval on the basis of their own. They will pass the ethical approvals of subcontracting clinics to the coordinator including their patient´s informed consent formular. In these centres patients' enrolment has not yet started and will start as recently as the valid ethics approvals are received.

2.5 MANAGING MODIFICATIONS TO CLINICAL STUDY PROTOCOL

All ethically relevant modifications of the clinical protocol will be submitted as an amendment to the local ethical committees for approval. If modifications should appear, the Ethical Board will commonly assess their relevance for notification as an amendment in the ethical approval. EU-relevant as well as local legislations and issues will therefore be respected. Approvals for these amendments will be collected by the Coordinator. This is valid for the clinical centers as well as their subcontracting partner clinics.

2.5.1 Tasks and responsibilities

The following table summarizes the project governance structure and the main responsibilities connected with the project Ethics Management.

Role	Type	Appointment	Responsibility
Ethical Board	Body	It includes the PIs of each clinical study participant site in the Project, appointed by the relevant responsible Partner, plus an Ethical Manager who chairs the Board.	It manages project's ethical issues (see DoA part A, WP1, task T1.4)

Role	Type	Appointment	Responsibility
Ethical Manager	person	Member of the Ethical Board	Monitors and addresses ethical issues in close cooperation with the Coodinator, collects ethical approvals and amendments, agreements and handling instructions
Coodinator	person	Chair of the project, Member of the Ethical Board	Monitors and addresses ethical issues in close cooperation with the Ethical Manager, collects ethical approvals and amendments, agreements and handling instructions
PIs	person	Representative of a clinical center and its subcontractors	Manages and ensures local ethical issues, ensures correctness in native language, refers all relevant documents to the Coodinator and Ethical Manager, addresses all discrepancy or eminent challenge to the Ethical Board
Subcontractor	clinic	Subcontractor of a specific clinical partner/PI	Manages and ensures local ethical issues, ensures correctness in native language, refers all relevant documents to the associated PI, who passes them to the Coodinator and Ethical Manager, addresses all discrepancy or eminent challenge to the Ethical Board by informing the associated PI, who is member of the ethical board
Local ethical committees	committee	Local commiteee	Reviews and approves the BD2Decide Project ethics and amendments for the specific local side

Table 2-2. BD2Decide Ethics Management roles and rsponsibilities

2.5.2 Ethical Board and Ethical Manager

The Ethical Board established by BD2Decide Consortium manages and monitors the fulfillment of the ethical requirements for BD2Decide clinical study execution in the Clinical Centres and for the patients' data management by technology partners, ensures that the appropriate ethical frameworks and procedures are in place, as illustrated in the DoA part B, section 5.

It includes the PI for each Clinical Centre in the project and at the subcontracting clinics, appointed by the relevant responsible Partners, as summarized in the following table.

The Ethical Manager, Dr. Kathrin Scheckenbach, MD, PhD is in charge of monitoring the adherence to all ethical aspects related to the clinical study execution based on given information and reports (if necessary translated into English) of all clinical partners.

Clinical Centre	Responsible Partner	PI
Milano	INT	Lisa Licitra
Parma	AOP	Tito Poli
Amsterdam	VUmc	Ruud Brakenhoff
Dusseldorf	UDUS	Katrhin Scheckenbach
Maastricht	MAASTRO	Philippe Lambin / Frank Hoebers
Lisbon (INT subcontractor)	INT	Lisa Licitra
Poznam (INT subcontractor)	INT	Lisa Licitra
ULM (UDUS subcontractor)	UDUS	Kathrin Scheckenbach / Rene Grässlin (ULM)

Table 2-3. The Ethics responsible organizations at BD2Decide Clinical Centres

2.5.3 PIs in each participating centre

As stated in the 5.2.5 of the BD2Decide DoA, the Principal Investigator at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, and possible risks and benefits of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient provides signed and dated informed consent before conducting any procedure specifically for the study.
- Ensure the original, signed ICF is/are stored locally in the Investigator's Study File.
- Ensure a copy of the signed ICF is given to the patient.

PIs in each Clinical Center ensured that a positive, valid ethical approval that covers the protocol of BD2Decide and respects local ethical demands is available and was sent to the Coordinator for collection.

Patient´s informed consent composed in compliance to the European Clinical Trials Directive (EC2001/20). Personal data will be managed according to Directive 95/46/EC and the relevant national application law. Since ethic proposals and patient´s informed consents are submitted in the country´s first language, the local PI is responsible, that the content of the ethical approval is correct and covers all needs of the BD2Decide Project based on the submitted grant and ongoing modifications. The same is valid in case of all kinds of necessary amendments.

PIs are responsible for the local pseudonymization of the data including imaging and biological specimen before provision to other partners.

They are responsible for keeping the local pseudonymization key and its correctness. Furthermore, they are responsible for guarding the data and regularly back-up it in an adequate back-up-system.

PIs must ensure an adequate information and training of local staff that is involved in and contributes to the study. Here the aspect of data management, as well as management of biologic samples and imaging and the pseudonymization strategy have to be addressed. He is responsible, that the patient´s subscribed informed consent is present and that its presence is documented correctly in the patients CRF. The electronic CRF in OpenClinica contains a field for the documentation of the presence of a valid patient´s informed consent to insure this.

PI´s ensure locally, that data-, imaging and specimen processing is performed like described in the dedicated documents (attached to this document).

Processing pathways have collectively been established for the clinical data (CRF), specimen processing for genetic analysis (INT), specimen processing for HPV analysis (VUmc) and the processing of imaging (MAASTRO, Fraunhofer, POLIMI, technical partners). Any discrepancy or eminent challenges are addressed by the partners to the Ethical Board, where a conjoint solution is aimed.

2.5.4 Monitoring and verification procedures

The Ethical Board is the heart of the ethical framework since the PIs of all clinical partners are presented. Major regulations for a coordinated safe handling of data, imaging and specimen are established in the ethical board. They are documented in collective agreements for data transfer (DTA) and material transfer (MTA) as well as process instructions for the handling and transport of specimen for HPV analysis, genetic analysis, data- (electronic CRF) and imaging transfer. Here also the execution of all data sources beyond the project and after the end of the project are regulated. All kind of data, materials and imaging data is strictly transferred outside the treating center in a pseudonymized way. The Ethical Board is addressed in case of any discrepancy or eminent challenge concerning the belongings of BD2Decide and attributed data. This is also true for the appearance of discrepancy or eminent challenges concerning clearly BD2Decide attributed data sources beyond and after the project.

The Coordinator and the Ethical Manager ensure that all ethical approvals of the clinical partners are present (attached to this document). During data collection in the electronic CRF, local PIs ensure the presence of the patient´s informed consent. Within the documentation, the Coordinator and the members of the Ethical Board can review the integrity of this information e.g. by a random inspection. Any discrepancy or eminent challenge are addressed to the Ethical board, where a conjoint solution is aimed.

All agreements and handling instructions needed to guarantee a correct data- imaging and material transfer respecting pseudonymization and ethical rules, are all time available for all partners in the password-secured OwnCloud platform of the BD2Decide Project.

3 MANAGEMENT OF BIOLOGICAL SPECIMENS

3.1 CONTEXT

Biologic specimens are needed for BD2Decide study execution. Their usage and possible transfer between one Institution (the PROVIDING PARTNER, i.e. the clinical centre custodian of the biologic specimen) and another (the RECEIVING PARTNER, i.e. the BD2Decide beneficiary entitled to process the biologic specimens for data extraction) is ruled in pseudonymized way under the informed consent signed by patients and by a Material Transfer Agreement (MTA) signed between the two involved beneficiaries.

Biological specimens are collected in each hospital as usual practice from tumor biopsies and tumor tissues when surgery is performed and are stored under formalin (FFPE). Only patients for whom this biologic materials are in sufficient quantity to maintain an adequate quota in the hospital will be selected for BD2Decide study. Pathologists in each participating hospital are responsible to guarantee this condition and to prepare the materials required for BD2Decide RNA sequencing and HPV status determination. A SOP has been defined as part of the study protocol for samples preparation, labeling and shipment, which is integral part of the MTA signed by the providing and by the receiving partners.

Biologic samples taken from the FFPE banks are provided by all participating hospitals (partners and subcontractors) to INT genetics laboratory, after encoding them with a numeric identifier automatically generated by BD2Decide and that does not allow to identify the patient identity (see section 4.3 for details).

The following uses of biologic specimens are foreseen in BD2Decide clinical study:

Description	Responsible partner (Receiving Partner)	Providing Partners
RNAseq processing genomic signature extraction from sections of FFPE tumor/biopsy specimen collected in each participating centre for retrospective and prospective patients; , HPV signature extraction for Oropharynx cancer FFPE specimen.	INT - Scientist: Loris De Cecco	AOP (T. Poli) INT (L. Licitra) VUmc (RH Brakenhoff) UDUS (K. Scheckenbach) MAASTRO (F. Hoebers)
HPV testing on OroPharyngeal cancers	VUmc - Scientist RH Brakenhoff	UDUS (K. Scheckenbach)

Table 3-1. Procedures requiring biologic specimens

3.2 RELEVANT ETHICS REGULATIONS

For what concerns data protection, we abide to the EU regulation for data privacy and on National regulations where these are more restrictive.

For what specifically concerns genomic tests and data management, the BD2Decide Consortium abides to the regulatory framework set by the European Medicines Agency (EMA) ICH guideline E18 on genomic sampling and management of genomic data[3]. This regulation addresses maintenance of samples integrity, samples quality and technical performance of assays. Genomic samples and data will be securely stored, maintained, and access controlled similar to non-genomic samples and health information. The main principles relate to management of specimens and management of genomic data extracted from biologic specimens.

3.2.1 Management of biologic specimens for genomic tests

1. ***standardization of procedures***: staff at all participating sites should be properly trained to use standardized procedures as described in the relevant SOP;
2. ***type of specimens*** to be collected should be compatible with the intended use;
3. ***data collection*** shall consider inter- and intra-subject variability in the context of the clinical study objectives (e.g. through patients inclusion/exclusion criteria);
4. ***specimen preservation conditions:*** accurately evaluate the impact of fixation and additives on the analytes of interest and the types of tests to be carried out prior to sample collection in a clinical study;
5. ***specimen stability and degradation***: take appropriate handling measures to prevent nucleic acid degradation and genomic profile alterations during sample collection and processing, optimize the time from specimen collection to freezing, fixation, or processing, as well as the storage time; monitor conditions of specimens storage and processing;
6. ***specimen volume and composition***: accurately size the specimens volumes in order to guarantee appropriate analysis;
7. ***genomic sample quality***: apply appropriate quality control methods to determine if the quality and quantity of the extracted nucleic acid targets are adequate for the defined downstream genomic testing to be performed;
8. ***sources of interference***: monitor potential sources of interference that might affect assays performances;
9. ***transport and shipment***: establish the appropriate transport conditions prior to sample shipment;
10. ***samples storage***: ensure that samples are appropriately stored until use and that residual aliquots are destroyed at the end of the study;
11. ***curation of samples inventory***: monitor and curate samples inventory relative to: consent for

[3] See http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2016/02/WC500200837.pdf

use of the samples, length of storage relative to the sample retention policy, and requests to withdraw samples or destroy them in case of patient's withdrawal from the study or end of the study.

3.3 BD2DECIDE ETHICS MANAGEMENT OF BIOLOGICAL SPECIMENS AND DERIVED GENOMIC DATA

The procedures for samples collection, preparation, storage, preservation during shipment, storage and maintenance at receiving partner's site, preparation for RNA sequencing, as well as for data management, follow the indications of the above mentioned EMA directive.

3.3.1 Processing of biologic specimens at the providing partner

The processing of biologic specimen at the providing partners' laboratories is performed in order to ensure:

1. quality of the portion of the biologic specimen used for BD2Decide

2. correct attribution of each specimen to the related patient/study subject

3. pseudonymization of the biologic samples and correct labeling

4. correct packaging aimed at ensuring quality and integrity of samples during shipment

5. adequate shipment procedures.

SOPs for genomic samples management has been agreed between INT (the partner performing RNA sequencing and genomic data extraction) and the providing partners VUmc, AOP, MAASTRO, UDUS and subcontracting hospitals.

A SOP is defined for samples preparation from FFPE specimens preserved at providing partners and for samples shipment to INT (protocol “SOP_procedures RNAseq_BD2decide”).

Sample handling is regulated in the commonly agreed MTA and handling instructions for genetic sampling and HPV sampling.

Pathologic samples for the BD2Decide project contains paraffin embedded tissue that was taken during tumor biopsy and/or oncologic surgery. Therefore, all samples are reviewed by local pathologists and classified as squamous cell carcinomas. Tissue samples used for analysis should contain at least 80% tumor tissue. Thus tumor parts fulfilling these criteria are isolated by macrodissection technique and sent by Providing Partners to Receiving Partners due to shipping protocols defined by the Receiving Partners according to their requirement. HPV sampling and shipping is described in the “Tissue protocol HPV testing BD2Decide” by VUmc.

Providing partners (AOP, MAASTRO, UDUS, VUmc) identify appropriate patients for the BD2Decide study by clinical parameters and the existence of appropriate imaging. After the patient´s informed consent is given or or for retrospective patient´s in some centers, waiver´s are verified, they address their local Dept. of Pathology for allocation of suitable patient´s samples.

After macrodissection and pseudonymization of the samples according to the locally stored pseudonymization key, samples are prepared and shipped according to the relevant SOP´s of Receiving Centers ("Tissue protocol HPV testing BDDecide" by VUmc, "SOP_procedures RNAseq_BD2decide" by INT) to the Receiving Centers. Receiving Centers only receive pseudonymized specimen, data and imaging that does not allow any backtracking of the patient´s identity.

The correct attribution of each sample to the patient is under the responsibility of pathologists at the providing partners' premises. An internal registry of all samples prepared and shipped is maintained and the link between each sample and the patient is ensured by an internal registry maintained by the pathologist and revised and monitored by the PI at the providing partner's.

For the correct attribution of each sample to the right patient, local Providing Partners sign the samples with the patient´s ID generated during the pseudonymization process of the BD2Decide project before sending the sample to the Receiving Partners. Each Providing Partner makes sure that a correct attribution takes place. Each Providing Partner safes the pseudonymization key locally and ensures a regular back-up in an adequate system.

Pseudonymization of the samples as a process takes place locally by the Providing Partners before the samples are transferred to the Receiving Partners. Receiving Partners receive only pseudonymized samples identified by the BD2Decide-dedicated pseudonymization key. Identification of the patient by person is not possible outside the treating, responsible clinical centers.

For correct packing and shipping, needed conditions are documented be Receiving Partners in specific protocols and handling instructions for Providing Partners. All Instructions are agreed with and provided to Providing Partners.

3.3.2 Processing of biologic specimens at the receiving partner

INT is the receiving partner for genomic tests (RNA sequencing) and HPV status assessment.

VUmc is the receiving partner for HPV immunohidstochemistry testing on UDUS biological specimens.

A SOP has been defined for samples management and processing (RNA sequencing) at INT receiving partner.

A SOP has been defined for samples management and processing (p53 stain etc.) at VUmc.

These SOPs are integral parts of the MTA signed by providing and receiving partners. These SOPs comply with EMA guidelines. The MTA and the relevant DTA comply with both EMA guidelines and data protection and data privacy regulations.

3.3.2.1 Management of specimens at INT

To ensure pseudonymization, upon arrival or extraction, a unique identification code connected with the single patient will be attributed to all the clinical samples included in the study and received from the participants. Aliquots will be prepared from samples using the bar-coding device of Twin-Helix that enables a computer recording and tracking. All the experimental and bioinformatics activities will be tracked using dedicated software for documental repository provided by IBM. The Samples will be stored in an alarmed -80°C freezer dedicated to the Dr Licitra studies.

The unused material and all the intermediate products, after experimental analysis and control of data quality, will be destroyed or sent back to the providers, according to the signed MTA.

3.3.2.2 Management of specimens at VUmc

Samples received at VUmc are pseudonymized by UDUS prior to shipment. VUmc will perform immunostaining tests which are not usual practice at UDUS and will not be performed by UDUS pathologists.

Local handling procedures for oropharyngeal and non-oropharyngeal samples in the Providing Center is similar to the handling of specimen for genomic data (described in 3.3.1). Transfer including needed shipping conditions and the samples needs for HPV diagnostics are described in detail in the "Tissue protocol HPV testing BD2Decide" provided by the Receiving Partner VUmc

Biologic specimens are stored at VUmc laboratories for the test execution only. Any residual samples will be destroyed after verification of the quality of the tests performed.

VUmc will perform the relevant immunostaining tests on samples and will send the test results back to UDUS. UDUS PI is responsible to insert the test results in BD2Decide repositories (OpenClinica or BD2Decide electronic health record system for prospective study).

3.4 MANAGEMENT OF BIOLOGIC SPECIMENS AT THE END OF BD2DECIDE STUDY

As defined in the MTA, all residual biologic specimens not used at the end of BD2Decide study must be destroyed. The materials might be maintained only on exception basis and upon specific written agreements between the two involved parties (Providing Partner and Receiving Partner). These written agreements have to be addressed to the Ethical Board and collected by the Coordinator and the Ethical Manager. The same is true for clinical partners and their subcontractors.

3.4.1 Management of genomic data by INT

Receiving Partners (INT) will perform RNAseq analysis of the provided, pseudonymized samples. The generated BAM files will be placed at a local server of the receiving partner INT for the duration of the project. The raw data is in the ownership of the Providing Partners and given to them for storage and care during and after the project. The Receiving Partner destroys the

unprocessed BAM files after they have been processed for the purposes of the BD2Decide project unless further agreements are performed in accordance with additional ethic approvals and in accordance with the needs of the BD2Decide project.

The BAM files will be processed locally at the Receiving Partner and the data needed for the BD2Decide analysis will be extracted. These data does not allow any identification of the patient and is therefore not classified as sensitive in respect to backtracking to the patient´s identification. BAM files will be manually (e.g. on hard disks) delivered and transferred to the hospital that sent the samples and will be deleted from INT server. Each Providing Partner will receive raw data of only their patients.

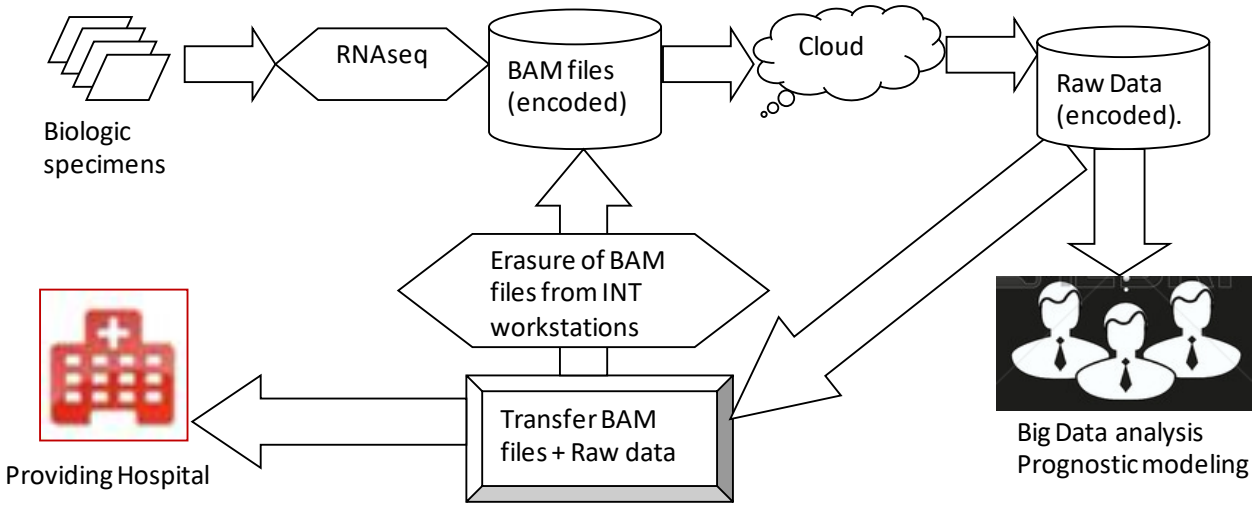

Figure 3-1. Scheme of the procedure for genomic data management by INT

For data transfer, no US-based cloud will be used. Raw data shall be kept locally in each Providing Center for a sufficient time period (e.g. 10 years in Italy, Germany) according to local laws and needs.

Since we plan to perform only partial sequencing, data resulting from this technique is not suitable for generating a genetic fingerprint of the patients, potentially allowing a patient´s referral. Primary sequencing data will not be shared.

Each center is the owner of the data and responsible for long-time storing. Furthermore, the responsible receiving partner (INT) only get biologic specimen of pseudonymized patients from providing partners with no chance of a backtracking of the data outside the center. This is regulated within the MTA and DTA between the partners.

For publications, only pseudonymized data is used and genetic information is limited to the belongings of modeling and the purpose of the project. Data is collectively published after statistical analysis and aggregation and accordingly modeling.

3.4.2 Responsibilities and methods of verification

The PI of receiving Institution (Receiving Scientist) must provide a written declaration to each Providing Partner Scientist that all residual materials has been destroyed or present a written

agreement between the concerned Providing Partner and Receiving Partner on an exception basis to maintain the material.

3.5 MANAGEMENT OF DIAGNOSTIC IMAGES

Diagnostic images are managed by the authorized radiologists at each participating centre. They are processed by radiologists to segment regions of interest (Tumor, lymph-nodes, other regions if applicable) and extract anatomic features by means of the Image Analysis Tools developed by Fraunhofer IGD in WP3.

Diagnostic images are downloaded from hospital PACS after undergoing removal of patient's identification information (e.g. Name, birth date, national insurance code, hospital code), as described in the following section 4.4. In case images are brought to the hospital by the patient, they are stored in a separate PACS, processed to remove patient's identification information and then transferred to the separate workstation used for Fraunhofer Image Analysis Tools execution.

The results of this processing are anonymized images, to which the B"2Decide Patient ID (see 4.3 below) is manually assigned by the radiologist. Images so processed are compliant with EU and National regulations for data protection and privacy.

Segmented images are then transferred via secure https protocols to POLIMI and MAASTRO for radiomics features extraction from MRI and CT scans respectively. Anonymized images might also be manually delivered by radiologists to POLIMI and MAASTRO researchers on digital supports if needed and agreed between parties. Copies of anonymized images are kept at each partricipating hospitals (as required in case of publications) and are also available on a shared repository managed by AII and ATC, for consultation by physicians.

The BD2Decide DTA and MTA regulate the transfer and use of diagnostic images during and after the end of the project.

3.6 ETHICS ASPECTS MONITORING AND VERIFICATION PROCEDURES

Ethic monitoring includes different levels:

1. General ethic approval by the ethic committees including protection of IT-related patient´s data
2. Local ethic monitoring within the clinical centers (Provider –related):
3. Good ethical governance of received data (Receiver-related):
4. Protection of the BD2Decide Data source to third parties within and after the project

The BD2Decied Project is based on ethic legislation of the EU and local authorities. These need a formal ethic framework that guarantees the basis for the ethically correct implementation of the project. The ethic approvals of each clinical center are therefore needed.

Here, each PI is responsible to write and submit an ethic proposal to the dedicated local Ethic Committee according to the BD2Decide proposal and its belongings. Changes should be respected and if needed added as an amendment. In each ethic proposal, underlying EU- and local laws and ethic principles must be respected. Since these ethic proposals and the associated patients informed consent and information forms are written in the local language, each PI is responsible for the correctness of the content of the ethic proposal that should transfer (pseudonymized data) can start after a valid ethic approval is received.

A patient information sheet is written in the local language and prepared in accordance with the ICH Note for Guidance on Good Clinical Practice (ICH, Topic E6, 1995). It will be provided for the purpose of obtaining informed consent. Approved ethic proposals and amendments should be passed to the Coordinator and the Ethic Manager, who collect them and check the totality.

If a further approval of the local patient´s data management is needed, the Coordinator and the Ethic Manager must be informed and this approval must also be passed to them for collection. In case of any discrepancy or eminent challenge, this must be addressed to the Coordinator and the Ethical Manager. Discrepancies and challenges that can be solved locally, should be solved locally. Any other case should also be addressed to the Ethical board, where a conjoint solution is aimed.

Subcontracting clinical partners are in first line supervised by the PIs of their contract partners. Here the local PI and the person in charge of the subcontracting institution (both partners) are responsible to write and submit an ethic proposal to the dedicated local Ethic Committee according to the BD2Decide proposal and its belongings. The clinical data, imaging and sample collection and transfer (pseudonymized data) can start after a valid ethic approval is received. Changes should be respected and if needed added as an amendment.

Already received ethic approvals from the PIs of the basic clinical centers are attached to this document.

Each PI is locally responsible that the BD2Decide study is performed due to the fixed ethical rules on the basis of the submitted ethic approval. In clinical routine, the PI is in charge to control this. Special attention should be drawn on the fact that all patient´s informed consents are assured and documented in the CRF correctly. Furthermore, the responsible handling of any patient´s associated data including only pseudonymized data and material transfer according to the taken agreements and handling instructions should be performed. Besides, no external partner or even third person should be allowed to enter local medical IT systems containing sensible patient´s data. This must also be assured by IT-related BD2Decide partners. Aberrations should be reported to the Coordinator and the Ethical manager. If they can be solved locally, they should be solved locally. Any other case should also be addressed to the Ethical board, where a conjoint solution is aimed.

Clinical data, imaging and specimen from subcontracting partners must be treated equally to basic clinical partners.

Receiving partners only receive pseudonymized data, that does not allow them any backtracking to the patient´s identity. In addition, they assure that also extensive data collection by radiomics or genetic analysis cannot be used for backtracking patient´s identity.

In genetics this is guaranteed by the fact, that only partial analysis of genomic information are performed. Genetic and imaging analysis will firstly be performed independently of clinical data sets and the unified in the BD2Decide database for general analysis.

By performing the analysis in 2 steps, a direct correlation of clinical and extensive imaging and genetic data should be avoided and therefore additionally prevent backtracking.

Third parties are not allowed to get insight to the whole BD2Decide dataset and they are not allowed to perform any analysis with the BD2Decide data beyond and/or after the project.

Data, imaging or material might be maintained and analyzed for other purposes only on exception basis and upon specific written agreements between the all involved parties (Providing Partners and Receiving Partners).

For any use of data generated for and within the project beyond BD2Decide, ethic agreements must be assured that fully cover these belongings. The Ethical Board of the BD2Decide Project has to be informed of and to agree to these activities.

4 ETHICAL ASPECTS OF PATIENTS' DATA MANAGEMENT

The management of patients' data is performed at two levels:

1. Internally to each participating clinical centre: to manage patients (prospective) and to ensure future use of BD2Decide in clinical practice: in this case data must be linked to the real patient and this link must be kept inside the hospital and managed according to the privacy regulations established by each hospital.
2. For the BD2Decide study and models and for research purposes: in this case patients' data are pseudonymized/encoded prior to be transferred to BD2Decide platform and data will not contain any personal information that might allow to identify the patient. Pseudonymization is performed by a neutral sequential ID-code that does not allow any retracing to the patient´s true identity. Since some patients were already part of prior studies (OraMod, NeoMark, MAASTRO etc.), previous patient´s ID´s are transferred internally to the BD2Decide-dedicated sequential ID-code which is used within the OpenClinica System.

4.1 LEGAL CONTEXT

The legal framework for patient's data management in multicentric clinical study is defined by the following regulations at EU and national level:

- Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.
- National directives on data privacy.
- Directive (EU) 2016/680 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data by competent authorities for the purposes of the prevention, investigation, detection or prosecution of criminal offences or the execution of criminal penalties, and on the free movement of such data, and repealing Council Framework Decision 2008/977/JHA.
- ICH guideline E18 on genomic sampling and management of genomic data issued by EMA.

4.1.1 Management citizens' health data

Citizens' health data are considered sensitive information and as such they need strict protection from undue disclosure and guarantee of patients' privacy.

The following principles shall apply:

1. no data that might disclose patient's identity must be disclosed to un-authorized persons; in clinical studies data shall be pseudonymized/encoded;
2. no data concerning race, sexual habits or religion shall be used or disclosed even in

pseudonymized form;

3. patients must provide written informed consent to the clinical study, upon being clearly informed by the PI at each participating centre concerning the scope, the effort required, any potential consequences of the research and on the right to withdraw anytime;
4. patients must clearly indicate to the PI whether they want to be informed in case of incidental findings arising from the study execution;
5. for genomic data handling, specific conditions as established by EMA guidelines shall apply.

4.1.2 Management of genomics data (EMA guidelines)

Genomics data are subject to more restrictive regulation as compared to patients' clinical data, as they contain extremely sensible information. Therefore pseudonymization procedures might not be sufficient to prevent undue disclosure of the patient's identity from genomic data. EMA guidelines indicate the following recommendations:

1. ***coding of data***: to decrease complexity and likelihood of error, single coding is recommended for genomic samples and data. Anonymization, as defined in ICH E15, is not recommended, because the process renders the ability to connect previously unlinked genomic data to phenotypic data impossible and it does not allow for sample destruction pursuant to withdrawal of consent or for end of study.
2. ***access to genomic samples*** and data shall be granted only to authorized personnel: contractual agreements shall be established to ensure strict control of access to data and samples.

4.2 CURRENT STATUS

As already stated in D1.1, procedures for electronic patients' data management in participating hospitals and for BD2Decide e-CRF have been established in agreement with the Legal Office of the Coordinator and of participating centres.

A Data Transfer Agreement is under signature to rule the responsibilities of each BD2Decide beneficiary concerning management and treatment of patients' pseudonymized data used for data analysis and modeling and for all the activities and tasks foreseen for BD2Decide (Ref. Technical Annex I - DoA).

These procedures comply with the Italian and EU regulations regarding privacy (i.e. non disclosure of personal information and in particular of sensitive data) and foresee the following:

- Data pseudonymization is applied to all patients' collected data.
- No full genomic profile is collected by BD2Decide, only partial genomic data are collected in anonymous modality.
- Imaging data are anonymized by the radiologists before image processing;

- Patients' data management remains under the responsibility of each participating hospital, who has received ethics approval for the BD2Decide clinical study, and patient's consent.
- Except of the gender and age, shared clinical data does not include identification-relevant information like name, address, birth date, phone numbers of the patient. The CRF is focused on data relevant for the description, classification, treatment and outcome of head and neck cancer and potentially affecting factors, which are essentially needed for performing the study.
- No partner outside the treating center will gain direct access to the local medical system.

4.3 DATA PSEUDONYMIZATION PROCEDURES

This paragraph describe the procedures adopted in the BD21Decide system for data anonymization

4.3.1 Linking pseudonymized data to real patients for care delivery

In the area of allowing clinicians to link pseudonymized data to real patients in the context of delivering care and treatment to Head and Neck cancer patients with the support of the BD2Decide platform, we introduce the following attributes:

- The BD2Decide patient ID: this is an identifier of the patient inside the BD2Decide platform, which is assigned once a patient is first introduced into the BD2Decide environment;
- The real name: this is real name of the patient, which is recorded at every visit of the patient in the clinical centre;
- The local patient ID: this is the identifier of the patient in the Hospital Information System (HIS) of the local clinical centre, which is automatically produced, when the patient with the real name is first introduced into the HIS.

4.3.1.1 Solutions examined

Towards linking these three different attributes, we have assessed a number of solutions. All these solutions are driven by the fact that we need to fulfil the following fundamental requirements:

- The BD2Decide patient ID, which is the identifier used internally in the BD2Decide platform for the patients of all clinical centres is unique;
- The patients' real name cannot be revealed to any system operating outside the network of the responsible clinical centre.

In the first solution we examined, the BD2Decide patient ID is automatically generated. More specifically, we assume that patient data already exists in a HIS, so the local patient ID is already in place. Outside the BD2D project, the clinicians know that the HIS has allocated a local ID for a patient real name. So, all specialties access the hospital systems with the local ID. For the retrospective and prospective studies, the clinicians enter the patient data into the platform, which creates the BD2Decide patient ID. Since, the platform offers different roles and discriminates between the users of each centre, this patient ID is global with BD2Decide, but it can be matched to

the real name of the patient, only by the clinical centre that introduced data into the platform to generate this ID. The clinicians are then responsible for creating a local file (i.e. in Microsoft Excel), which maintains the link of the patient real name, the local patient ID and the reference patient ID in the BD2Decide project. This file is locally maintained within the network of each clinical centre. This file can then be used by all the specialties of the clinical centre with a particular role in the use of the BD2Decide platform.

In order to read or update the patient data in the BD2Decide platform, one uses the local file to match a real name or local patient ID with the BD2Decide patient ID. By entering this ID into the interfaces of the BD2Decide platform, one can have access to the data of the specific patient. The platform will employ authentication and authorisation procedures for role-based access to the pseudonymized patient data, so depending on the registered user, one could navigate to the whole dataset or a subset of this.

The other solutions we examined assume that the clinicians manually enter an ID into the platform for the BD2Decide patient ID, which can be either the local patient ID or any arbitrary number. Since the BD2Decide platform knows that the registered user belongs to a clinical centre, when the user records the patient ID, the platform adds a 3-digit prefix with the initials of the centre.

In both solutions, the association of a real name with a BD2Decide patient ID should be maintained inside the clinical centre and by no means should we allow the clinicians to submit real names to the BD2Decide User Interfaces and, in turn, the platform to translate internally to a BD2Decide patient ID.

4.3.1.2 Responsibilities and verification

ATC, as the ICT provider of the corresponding components of the platform for the eCRF based pseudonymized data, is responsible for the proper generation of the BD2Decide patient ID and the maintenance of this data in the platform. ATC implements the respective authentication mechanisms to allow clinicians to access pseudonymized data, according to specific rules. The security measures applied by ATC to the pseudonymized patients' data are summarised in the following section.

4.3.2 ATC security measures in the BD2Decide platform

Basic principles

Personal data undergoing processing will be kept and controlled in such a way as to minimise, by means of suitable preventative security measures, the risk of their destruction or loss, whether by accident or not, of unauthorized access to the data or of processing operations that are either unlawful or inconsistent with the purposes for which the data have been collected.

Processing personal data by electronic means will only be allowed if the security measures referred to below are adopted in accordance with the privacy protection laws and regulations established at EU and at each Country level:

a. computerised authentication;

b. implementation of authentication credentials management procedures;

c. use of an authorisation system;

d. protection of electronic means and data against unlawful data processing operations and unauthorised access;

e. implementation of procedures for safekeeping backup copies and restoring data and system availability;

f. implementation of identification codes for specific processing operations performed by health care bodies in respect of data disclosing health and sex life.

Purpose of data collection in BD2Decide

ATC is developing the patients' documentation system (PDS) and the clinical decision support system (CDSS) through on premise deployment of relevant technologies and software solutions for collecting, managing, processing and storing pseudonymized personal data for the patients participating in the clinical studies of the BD2Decide clinical research centres. According to the established regulations, ATC is acting as a Data Processor, collecting and processing pseudonymized patients' data, as dictated by the BD2Decide Clinical Organisations, who are Data Controllers.

The corresponding data will be used only for the purposes of the BD2Decide project, as they have been described in the H2020-PHC-2015-689715 BD2Decide Grant Agreement and the associated Consortium Agreement. ATC will then use the pseudonymized data, from patients that have already signed a consent form with their clinical centres, for:

a) administering PDS and CDSS;

b) allowing doctors to browse pseudonymized data for the clinical status of patients;

c) enabling the execution of prediction analysis and prognostic models for Stage III and IV Head and Neck Cancer patients;

d) enhancing the co-decision process between the physicians and their patients on the appropriate treatment to be followed;

e) estimating the life expectancy rate for the patients and comparing it for different prediction models;

f) enhancing predictions by aggregating the pseudonymized patients' data with other big data, such as publicly available population data;

g) facilitating the implementation of the researchers' functionalities, as they are offered by the Visual Analytics Tool, developed by UPM.

Data storage

The BD2Decide software solutions, which ATC is implementing, will collect the pseudonymized patient's data that are indicated in the electronic Clinical Record Format of the project. The collected data shall not lead to the identification of any patient directly or infer to a patient through any other data combination. In that respect, ATC hosts and maintains pseudonymized patient data,

which cannot be considered either as personal or sensitive. In any case, ATC is harvesting the BD2Decide data as being personal data, thus the appropriate security mechanisms to protect the deployment of the BD2Decide solution are deployed by ATC.

The tools will process and store this data in the ATC' private cloud infrastructure, which is set up at ATC premises. This infrastructure consists of powerful Intel platform servers, suitable high-performance storage devices, firewall hardware and software and networking equipment combining technologies to provide performance and flexibility. To this end, the deployment of the BD2Decide solution follows the security policies and procedures being applied by ATC, in order to manage any personal or sensitive information required by the project. The storage area of the BD2Decide tools will be implementing backup and restore mechanisms to ensure continuity in the provision of the BD2Decide services.

Data retention and deletion

ATC stores the data collected by the clinical partners only for as long as it is necessary for the delivery of the services offered through PDS and CDSS. Apart from where the law stipulates a specific period, we retain the pseudonymised data for the BD2Decide project period, which is until December 2018, considering also an extension of this period by 90 days to facilitate the demonstration of the tools during the BD2Decide final review meeting. In compliance to our legal obligations with respect to the retention and deletion of personal information, in BD2Decide we set out specific conditions for our data retention policy and procedures for the BD2Decide pseudonymized data.

After the expiration of the BD2Decide data retention period, all the patients' pseudonymized data will be deleted from the ATC infrastructure, including any backups. By default, the retention policy of tape backups of ATC currently cannot exceed the 5 weeks. Furthermore, specific project data will be deleted following the written request from any Consortium partner, subject to the provisions of the BD2Decide Consortium Agreement.

Data security and transfers

ATC is employing the appropriate technical and organisational precautions to prevent the loss, misuse or alteration of any personal information or pseudonymized data used in the BD2Decide project. All the legally assigned BD2Decide representatives that have access to the project data stored into the ATC infrastructure are responsible for protecting the credentials they use for accessing PDS and CDSS and keeping their password confidential.

Access to the BD2Decide data is allowed through standardised technologies, developed for the project services. Specific user authentication and authorisation mechanisms are employed on the service and data layers of the DB2Decide solution that allow role-based access to the pseudonymized data. According to the operations foreseen in the project, the data collected from the ATC software may be transferred to the BD2Decide big data infrastructure, managed by All-in-Image. Secure technical interfaces allow transferring the BD2Decide data to this infrastructure through secure HTTP protocols.

Any other transfer is forbidden.

Data access rights and third parties

In order to safeguard security of the project pseudonymized patients' information, a number of security measures are indicated. To this end, all BD2Decide participants that need access to the pseudonymized information stored in ATC for the implementation of the BD2Decide project are bounded by the Consortium Agreement for not disclosing any information outside the project. ATC is using standardised technologies for secure storage, delivery and access of personal information, as well as managing the rights of the users. In this way, there is complete guarantee that the accessed, delivered, stored and transmitted information will be managed by the right persons, with well-defined rights, at the right time.

Through the use of advanced firewall operations, the ATC network prevents the connection to open network ports, and exchange of data will be through consortium known ports, protected via password protected mechanisms and strict IP filtering rules. The BD2Decide platform, including PDS and CDSS, will issue server side SSL certificates to validate secure connection of the BD2Decide users to the software developed by ATC. In more details, within BD2Decide ATC is developing the following data access mechanisms:

- Security at the Application layer: this applies to the end users of the BD2Decide tools deployed at ATC premises, namely clinicians, physicians, clinical researchers, etc., as well as the software of other partners interfacing with the ATC tools, such as UPM for the Visual Analytics tool and All-in-Image for the big data infrastructure. These stakeholders enter or read pseudonymized patient data through the relevant software, which is released as a secure Web application. In this application, access to the provided functionalities is granted through HTTPS, while each user has their own credentials and defined role.
- Security at the Transport layer: The server hosting the BD2Decide tools will be certified through (self-signed) SSL certificates to be a trusted information source.
- Security at the Network layer: If requested, and as long as it can be supported by the clinical partners, ATC may introduce an additional level of security by enforcing IP filtering to allow access to the BD2Decide tools hosted within the ATC network.

4.3.2.1 Responsibilities

In accordance to the obligations from the implementation of the BD2Decide Grant Agreement, all the BD2Decide Consortium members assign authorised personnel to access ATC software and the collected and processed data, subject to their role in the project.

4.4 ANONYMIZATION OF DIAGNOSTIC IMAGES

Clinical partners identify the relevant imaging within their centers. Providing partners perform image segmentation locally, using the segmentation software distributed by the Fraunhofer Institute.

The Fraunhofer software is locally installed in the centers of the clinical partners. There is no direct IT-link between the hospital´s medical data bank of Providing Clinical Partners and Receiving Partners outside the clinical centers. Imaging anonymization is performed within the clinical centers

of Providing Partners before passing the segmented imaging to Receiving Partners. Therefore, receiving Partners are not able to conclude to the patient´s identity by received imaging. For imaging anonymization a locally installed software is used. Local anonymization software routinely provided by the Dept. of Radiology or alternatively software provided by technical partners (e.g. Fraunhofer Institute) is locally used. Imaging is only passed to any partner outside the treating center in a anonymized way, that does not allow any backtracking.

Diagnostic images and extracted data, passed to the Receiving Partners is primarily not linked to the clinical data of the patients. Unlinked imaging data is analyzed by the Radiomics software by the Receiving Partners (MAASTRO, POLIMI). After analysis, radiomic data is integrated into the BD2Decide software system and therefore linked to genetic and clinical data for modeling. This strategy helps to prevents patient´s identification because of imaging and it prevents the usage of clinically linked imaging data by third parties (e.g. Oncoradiomics Company). All PIs guarantee that third parties have no access to the BD2Decide database.

During modeling, anonymizd values, extracted from imaging data is linked to pseudonymized clinical data and pseudonymized extracted genetic features by their pseudonymization that is able to link the pre-analyzed data sources. Since all data sources are pre-analyzed, the extracted data composition is not sufficient to allow any retracing of the patient´s identity only by this combined, pseudonymized data.

The imaging process represents a main component of the BD2Decide system. Raw images are initially stored locally in the PACS (Picture Archiving and Communication System) on each clinical center. The raw images are stored in DICOM (http://dicom.nema.org/standard.html) format. The images in DICOM format include sensitive information about patients, such as name, gender, age and city. This information are included in the header tags of the images files (metadata) and also in the image itself. Due to the risk of patient identification it is necessary that the images acquired and treated by the BD2Decide system are previously anonymized.

The process of anonymization consists in deleting patients' sensitive and identity information included in the images and in the metadata of the image files. In order to eliminating the information contained in the image itself, a printed text detection is performed (Figure 4-1). The text detection is executed by processing the digital images and comparing the characteristics of the regions of interest.

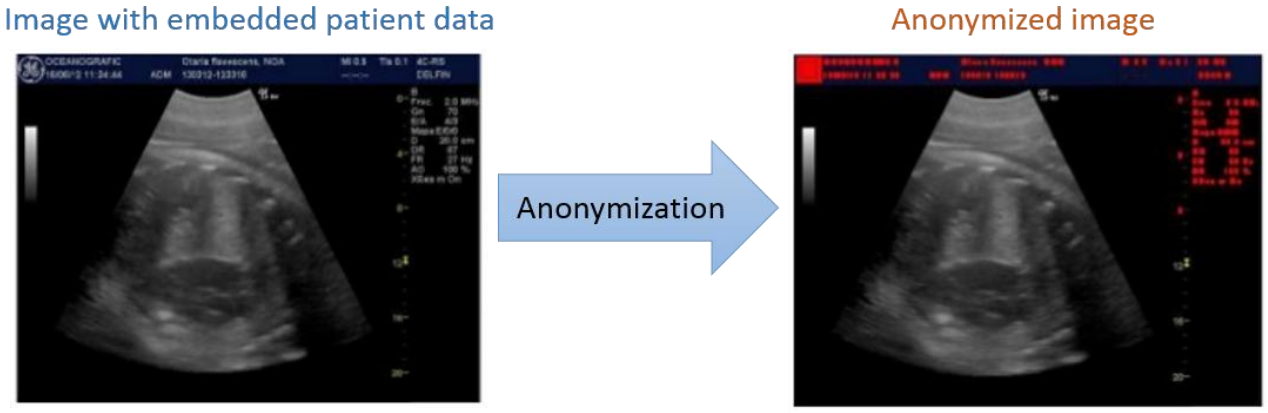

Figure 4-1. Image anonymization

The anonymization process is executed locally by a radiologist, through internals software tools, installed on clinical centers. In Parma clinical center, the software SUITESTENSA (http://www.esaote.com/es-ES/healthcare-it/software-healthcare-it/p/suitestensa-ris-pacs/) is applied to raw images. SUITESTENSA is an information and imaging management platform specifically dedicated to Radiology, Nuclear Medicine, Radiotherapy, Breast Medicine, Interventional Radio, Orthopedics and Operating Room, which provide administrative, reporting and post-processing tools. This solution is based on web-enabled technology and support standard communication protocols, such as DICOM 3.0, HL7 and FDA-XML. The use of established standards provides systems' interoperability and avoiding data duplication.

Similar tools to SUITESTENSA are used in the other clinical centers. The tools include functionalities to export images and to eliminate all sensitive data (DICOM tags) linked to the patient.

Once the images are anonymized, an internal algorithm is implemented to cross the data and to present them to professionals. In particular, few demographic data (i.e. age and gender) and patient' clinical center are available to the technical partners, allowing patient identity protection within the BD2Decide system. The image anonymization process for Parma clinical center is represented Figure 4-2.

Patients' images are encoded and identified to a specific and unique patient identifier (patient ID), defined into BD2Decide system. The patient ID is automatically generated by OpenClinica for the retrospective study and by the CDSS for the prospective study.

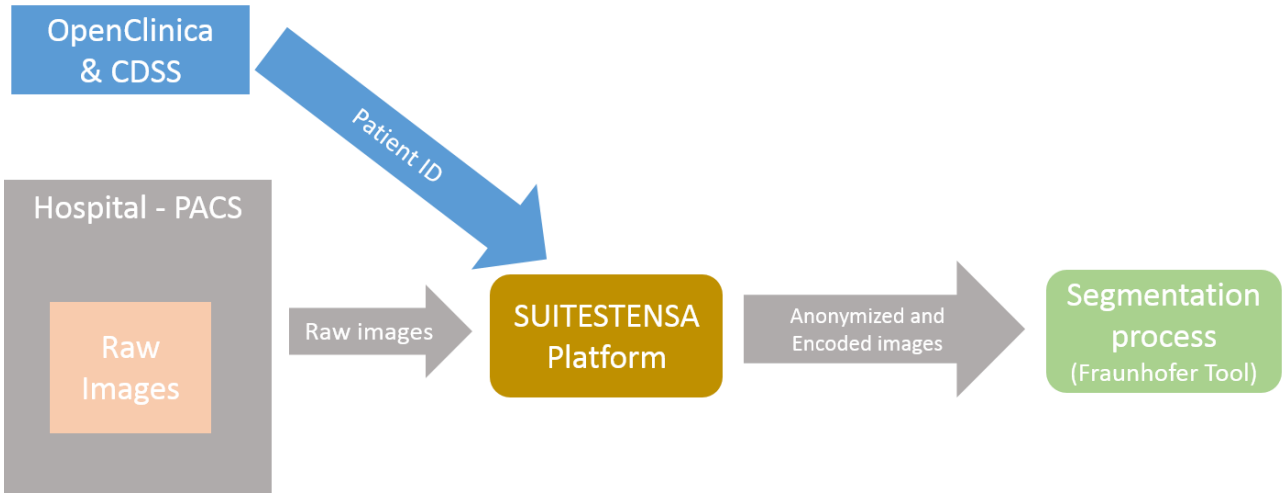

Figure 4-2. Example of image anonymization in Parma center

4.4.1 Responsibilities and methods of verification

Regarding responsibilities, the patients' data is collected by the clinical centres. Each center has assigned the appropriate personnel to enter data for retrospective and prospective studies into the BD2Decide platform, in the form of electronic Clinical Format Record. These personnel are responsible for the validation of data inserted into the platform.

4.5 DATA INTEGRITY MANAGEMENT

4.5.1 Correspondence of data to the right patients

Correspondence of data to patients is responsibility of PIs at each participating hospital. In case of biologic materials, the responsibility lays with the pathologists appointed by providing partners who must ensure appropriate labeling of biological specimens before packaging and shipment. At the receiving partner's premises, the responsible investigator (as defined in the relevant SOP and MTA) are in charge of correctly assigning the data originated by the biomolecular/genomic analysis of the biological specimens to the relevant patients by means of the unique ID assigned by BD2Decide.

The same applies to the segmented diagnostic images and related radiomics data generated by MAASTRO form CTs and by POLIMI from MRI scans.

From a technical viewpoint, the PI of each participating hospital is required to check and approve data inserted in the e-CRF (OpenClinica) and in BD2Decide repositories by digitally "closing" patients' records from his/her access account.

4.5.1 Data Base integrity

The integrity of the BD2Decide DB will be ensured by a periodic verification of data present in the data bases. These verifications will be mandatory before data usage by models and big data analytics systems.

Data preservation is ensured by the backup and restore procedures established for the project.

4.5.2 Responsibilities and methods of verification

Responsibilities and methods of verification have been described in 2.5.4, 3.4.2, 3.6 and in above paragraphs of the current document section.

For data integrity, Data Managers appointed in each participating hospitals are in charge of this verification and must report any data inconsistencies to the relevant PIs. The PIs of each participating hospital will immediately activate the restore procedures, if relevant, and will inform technology partners of possible data corruption issues.

4.6 BACKUP AND RECOVERY PROCEDURES

It any partner notices data loss or unauthorized data use in any respect concerning the BD2Decide Project, he should directly inform the Coordinator and the Ethical Managers. Local discrepancies may be solved locally. General discrepancies should be solved collectively within the Ethical Board.

Backups of data will be performed in each participating hospital as established by internal procedures. For the OpenClinica datasets, backups will be performed at least twice/month. Because patients' data are collected and stored at each hospital site, manual integration of missing data from

last backup will be possible.

In particular for genomic data, a mirroring procedure has been established at INT to maintain a daily copy of raw data on a second NAS dedicated workstation. Copies of BAM files are stored at each hospital premises.

4.6.1 Responsibilities and methods of verification

Each PI has to assure that the pseudonymization key is safely stored at only his institution. He has to take care of the patient´s data locally and reassure that the right and correctly attributed data is integrated into the BD2Decide system. The same is valid for imaging data and biologic samples. The local PI also has to reassure a regularly up-dated local backup system for the data so that no data loss should appear. As far as pseudonymized data, imaging or biologic samples are transferred from a Providing Partner to a Receiving Partner, the Receiving Partner is in duty to protect the commissioned data, imaging and sample as well as the obtained research results (raw data and processed data). The Receiving partner also has to provide a functional, regularly up-dated backup system. Third parties should never let unauthorized insight in or even transfer of BD2Decide attributed data. This point is even more to stress for data, commissioned of Providing Partners to Receiving Partners.

For backups and restore procedures the following responsibilities are set:

- Clinical partners (PIs) must maintain copies of patients' data in the hospital premises.
- Data hosting partners (ATC for OpenClinica, partner to be defined for BD2Decide CDSS datasets) are responsible to establish periodic (at least weekly) backups and restore procedures.
- INT is responsible to mirror genomic raw data.
- MAASTRO and POLIMI are responsible to correctly associate radiomics data to the patient ID indicated in the diagnostic images used for radiomics features extraction and to provide copies of extracted data to each participating hospital.

4.7 PATIENT'S WITHDRAWAL AND DATA ERASURE

Each patient of the study can withdraw his participation at any time of the study without mentioning any reason for this. The local PIs, who are the sole to able to identify the pseudonymized patient´s data, should correspond it to the Coordinator and should make sure that the patient´s pseudonymized data and imaging are identified and executed from the BD2Decide data bank. Also the biological sample of the patient must be removed and destroyed as well as the extracted data (HPV, genomics). It must be reassured that the patient cannot have any disadvantage neither in clinical handling and treatment because of his withdrawal.

4.7.1 Responsibilities and methods of verification

Responsibilities and methods of verification are described in 3.5 and are established in MTA and DTA. The PIs of each participating hospitals must ensure that data and materials are destroyed.

4.8 MANAGEMENT OF DATA AT THE END OF THE PROJECT

Data, imaging and biological specimen are belonging and in the responsibility of the clinical centers, providing them. All clinical data, imaging and biological samples or data generated out of them (e.g. genetics) must only be used for the needs of the BD2Decide project. The data and materials might be maintained or be used for research after or beyond BD2Decide only on exception basis and upon specific written agreements between the two involved parties (Providing Partner and Receiving Partner). Here ethical aspects have to be respected and if necessary additional ethic approvals and/or informed patient´s consents must be obtained.

The same is true for the use of clinical data, imaging and biologic materials and data generated by third parties. The coordinator should be informed of the use of data dedicated to the BD2Decide project and should get into contact with affected partners if necessary.

If no additional agreements are taken, the pseudonymized clinical and pseudonymized, edited imaging data have to be saved for 10 years. Afterward both data sources should be erased. Biological samples should be destroyed after the project unless other agreements between the involved partners (Providing and Receiving partner) are confirmed.

Ref. DTA and Ethics section 5 of DoA.

ANNEX A. TEMPLATE FOR INFORMED CONSENT AT PARTICIPATING HOSPITALS

We propose here the ICF standard template used by INT, which has been adapted by other participating hospitals, according to the local requirements set by their Ethics Committees.

Study name: A Prospective Observational Study for the Development and Validation of New Prognostic Models in Head and Neck Cancer Patients

Principal investigator: Dr. Lisa Licitra, MD (PI of other hospitals)

Form n. 1

STUDY INFORMATION FOR THE PATIENT

This module will be delivered to you well in advance of your final decision,
It provides essential information on the investigational study that you are asked to participate.
It is important that you read this information and that you discuss with your doctor
before signing the consent to participation in the study
(Form no. 2, "Informed Consent for Study Enrolment ").
The patient may withdraw his consent at any time.

Introduction

The head & neck medical oncology department of the National Cancer Institute in Milan (this is replaced by the name of other hospitals) has promoted this study to identify clinical, radiological and biological factors that may influence patient's prognosis in order to select subgroups of patients for the most appropriate treatment for maximize its benefits in the future. The identification of factors related to your clinical history, the treatments you have received, the detection of alterations of your genes and the characteristics of the microenvironment in which tumors grow might be a valuable aid to your doctors in order to better select patients who can benefit of anti-cancer treatments currently available.

Involved population

Eligible patients for this study suffer from locally advanced squamous cell carcinomas of the head and neck who are candidate to curative treatment with a combination of radiation, chemotherapy and surgery.

Study proposal

The study aims to identify factors or combinations of factors related to tumor prognosis and response to treatment able to influence disease history. There are no benefits for you, but the scientific knowledge which will be derived from this research could help, in the near future, to improve and optimize the possibilities for cancer treatment.

Personal data collection and biological samples

The study aims to collect and analyze patient's characteristics of the aforementioned population. Available data will be collected from medical records and all paper material and / or digital attachments of the clinical chart. Radiological information will be also collected.

The study duration is not standardized since it will depend on the time required to complete the data collection.

Cyto-histological samples from your archival tumor tissue already available will be simultaneously stored. These samples will be used to evaluate the biological characteristics of the tumor such as the presence of genetic alterations or viral infections related to malignant disease (eg. HPV infection).

It will be assigned a serial number identifying these specimens and only the medical staff will be able to associate it with you.

Participation in the study will produce no change in the current practice and also no additional diagnostic or monitoring procedure will be performed.

You will be asked to fill in a questionnaire investigating your quality of life at the beginning of the study and one year later.

The study will be conducted in accordance with the instructions contained in the "Recommendations to guide physicians in biomedical research involving human subjects", in accordance with the Helsinki Declaration of the World Medical Association and the rules of "Good Clinical Practice" issued by the European Union and transposed by the Italian Government.

Your biological samples will be stored at the Fondazione IRCCS Istituto Nazionale dei Tumori in Milan and at the Department of Otolaryngology and Head and Neck Surgery of the District, VUmc Institute, in Amsterdam.

The stored material, in compliance with the Italian Privacy Act, will be used exclusively for scientific research purposes, subject to the prior approval of the Ethics Committee of the National Cancer Institute of Milan (relevant Ethics Committee); it will never be used for profit and / or trade.

Your personal data (age, sex, medical history, previous or recurrent infectious diseases, allergies, medications), to the exclusion of your name, and those related to the history of your disease (stage, histological type, treatments performed, progression dates and follow-up) will be collected, registered and linked to information related to your biological material. Sample collection and processing of your data will be made upon approval by the Ethics Committee only after you have read, understood and signed the Informed Consent Form. Every patient who agrees to participate must give their written consent to the study, while asking all the required explanations to the doctor in charge, in order to understand all needed information.

By signing this informed consent, you agree that researchers at the National Cancer Institute of Milan use anonymously your biological sample and your personal data for research purposes.

Potential disadvantages

Your participation in the study does not involve predictable side effects.

Your participating is absolutely volunteer; at any time you have the ability to revoke your consent without providing explanations nor lose any rights.

Insurance

Given the observational nature of the study, the insurance policy provided by the Foundation ensures appropriate coverage, under current legislation.

Safeguards to protect the patient participating in the clinical study

This study was approved by the Independent Ethics Committee at the National Cancer Institute of Milan (other Ethics Committees of participating hospitals).

Samples will be processed, stored and analyzed under the responsibility of: Dr. Silvana Canevari and Dr. Loris De Cecco, as regards of genomic analysis, at the Laboratory of S.S. Service Functional Genomics and bio-informatics, IRCCS Foundation, National Cancer Institute, via Venezian, 1 Milan.

Dr. RH Brakenhoff, as regards the analysis to detect the presence of viral infections (HPV), at the Department of Otolaryngology and Head and Neck Surgery of the District, rm ZH 1 D 116, PO Box 7057, 1007 MB Amsterdam.

Your participation in the study is totally free. This means that you can freely decide not to participate in the study, therefore, not to sign this agreement, without affecting in any way the assistance you will receive at that institution.

A copy of this information form and a copy of any Consent will be given to the patient who agrees to participate in the study.

Information and expression of consent to the processing of personal data

(Pursuant to Resolution 52 of 24/7/2008 *Guidelines for processing of personal data in the context of clinical trials*)

Processing Controllers and Related Issues

The National Cancer Institute in Milan (other participating hospital) will process your personal data, particularly those on health, and only to the extent that are essential to the objective of the study solely on the basis of the realization of the study.

The updated list of those responsible for processing the data of patients participating in the study and all subjects who treat them - including analytical laboratories - is available and at your request, the doctor responsible of the study will provide it to you.

Nature of the data

The researcher involved in the study will identify you with a code: the data relating to you collected during the study (eg. date of birth, gender, your weight and your height etc, with the exception of your name), will be recorded, processed and stored together with this code. Only doctors and authorized entities will be allowed to link this code to your name.

Methods of data elaboration

The data, processed using electronic tools, will be disclosed only in strictly anonymous form, such as through scientific papers, statistics and scientific conferences. Your participation in the study implies that, in accordance with legislation on clinical trials of medicinal products, the personnel involved in the study, the Ethics Committee and the Italian and foreign health authorities will know the data that concern you, also those included in yours original clinical documentations, in such a way as to guarantee the confidentiality of your identity.

Exercise of your rights

You may exercise the rights under Art. 7 of the Code (eg. Access to your personal data, integrate, update, correct and object to their treatment for legitimate reasons, etc.) Applying directly to the Ethics Committee of the National Cancer Institute in Milan (other participating hospital).

You may withdraw your participation from the study at any time and without giving any reason: in this case, the biological samples related to you will be destroyed. No further data will be also collected; those data already collected will be used without altering the study results.

By providing your written consent, you authorize those who are involved in the study (medical staff, data managers, statisticians, inspection staff of regulatory bodies and those enabled by the study protocol and / or by the current regulations) to manage your biological samples and health information for the purposes of the study.

Any information about yourself will be published only in anonymous form, carefully and rigorously avoiding any details that might in some way allow third parties to trace your identity. Moreover, your data will be conserved in accordance with the security measures provided by the Code.

National Cancer Institute Milan IRCCS foundation protocol number: Prot. INT 65/16 -66/16 (other reference protocol for other participating hospitals).

Form n. 2

Study name: A Retrospective Observational Study for the Development and Validation of New Prognostic Models in Head and Neck Cancer Patients

Principal investigator: Dr. Lisa Licitra, MD (other PI for other participating hospital)

INFORMED CONSENT FOR STUDY ENROLMENT

This form must be signed by you only if you decide to participate to the study.
It is important *that you have thoroughly discussed with your doctor before signing this consent.*

The patient may withdraw his consent at any time.

I declare that I have been fully informed about the aforementioned clinical trial, that I have read the Study information for the Patient form

on…../…../…….

I got a copy for my records, and I have discussed adequately with my Doctors involved in this study,

on …../…../…….

at ……..;

2) I declare to be aware of the advantages and potential disadvantages linked to the object of the study;

3) I give my free and informed consent to take part in the aforementioned clinical trial;

4) I authorize the collection, storage and use of biological samples as previously detailed;

5) I authorize, for the purpose of this clinical study, the management of data regarding myself, in printed and electronic form, in compliance with current regulations, according to, among other things, of Italian Legislative Decree no. 196/2003 and subsequent amendments to complement the consent I have already subscribed to the processing of sensitive data at the Istituto Nazionale Tumori in Milan;

□ I authorize

□ I do not authorize

to provide to my general practitioner,

dr. ....

news about my participation in this clinical study.

Signature of Patient .....

Name of the Patient .....
Date: ... ../ ... ../ .....

Signature of the Legal Representative or Guardian ....

(if appropriate)

Name. .....

Date: ... ../ ... ../ .....

Signature of Witness) ....
(if appropriate
Name. ....

Date: ... ../ ... ../ .....

Signature of Witness..... .....
(if appropriate)
Name. ....

Date: ... ../ ... ../ .....

Researcher signature ....

Name. ....

Date: ... ../ ... ../ .....

ICF by UDUS

Patienteninformation

Sehr geehrte Patientin, sehr geehrter Patient!

Sie werden gegenwärtig als Patient der Hals-, Nasen- und Ohrenklinik (HNO-Klinik) am Uniklinikum Düsseldorf ärztlich behandelt. Das Uniklinikum Düsseldorf betreibt eine Biobank an der der Fachbereich HNO-Klinik beteiligt ist. Bei dieser Biobank handelt es sich um eine Sammlung von menschlichen Biomaterialien wie Blut, Urin oder Gewebe, verknüpft mit ausgewählten medizinischen Daten. Die Hals-Nasen- und Ohrenklinik bildet einen fachspezifischen Anteil dieser Biobank.

Die Untersuchung von menschlichen Biomaterialien und die Analyse der daraus gewonnenen oder zu gewinnenden Daten sind zu einem wichtigen Instrument medizinischer Forschung geworden. Deshalb fragen wir unsere Patienten und daher auch Sie, ob sie bereit sind, uns bestimmte Körpermaterialien und Daten für die Forschung zur Verfügung zu stellen. **Ihre Teilnahme ist völlig freiwillig. Soweit Sie sich nicht beteiligen möchten oder Ihre Zustimmung später widerrufen möchten, erwachsen Ihnen daraus keine Nachteile.**

Im Folgenden informieren wir Sie über die Ziele der Biobank des Uniklinikums Düsseldorf (Fachbereich HNO-Klinik), die Verfahrensweisen und die Maßnahmen zum Schutz Ihrer personenbezogenen Daten, damit Sie sich auf dieser Grundlage Ihre eigene Meinung bilden und eine Entscheidung treffen können.
Sollte Ihnen etwas unklar sein, fragen Sie bitte Ihren behandelnden Arzt bzw. Ihren Studienarzt, bevor Sie Ihre Zustimmung erteilen. Sie können sich wegen Rückfragen auch zu einem späteren Zeitpunkt an jeden Arzt der HNO-Klinik wenden.

1. Ziele der Biobank
Die Biobank des Uniklinikums Düsseldorf (Fachbereich HNO-Klinik) dient der Förderung medizinischer Forschung. In der Biobank werden Biomaterialien und ausgewählte Daten langfristig aufbewahrt und für die Forschung zur Verfügung gestellt, um die Vorbeugung, Erkennung und Behandlung von Erkrankungen zu verbessern. Innerhalb der HNO-Klinik beschäftigen wir uns in unterschiedlichen Arbeitsgruppen im Speziellen mit der Entstehung, Verbreitung und Behandlung von Tumoren und Entzündungen im Kopf-Hals-Bereich sowie, immunologischen Reaktionen und Möglichkeiten der Gewebemodulation im Kopf-Hals-Bereich. Ausserdem wird die genetische Veranlagung zur Ausbildung von Erkrankungen im Kopf-Hals-Bereich, wie z.B. Tumoren, Entzündungen (Allergie, Nasennebenhöhlenentzündungen) oder Hörstörungen untersucht.

2. Um welche Art von Biomaterialien und Daten handelt es sich?

Bei dem Biomaterial handelt es sich um Gewebe und Körperflüssigkeiten, die im Laufe Ihres derzeitigen Krankenhausaufenthaltes zum Zweck der Untersuchung/Behandlung entnommen, dafür jedoch nicht mehr benötigt werden und daher ansonsten vernichtet würden.
Hinzu kommen Blutproben (bis zu 20 ml), Schleimhautabstriche des oberen Luft-Atemtraktes und Sekretproben aus der Nase, den Nasennebenhöhlen

Hals-,
Direkt
Univ.-F
Sekret
Frau S
Tel:
Fax:
Escher
Frau B
Tel:
Fax:
Beate.
Stellv.
Prof. D
Sekret
Herr P
Tel:
Fax:
Patrick
Gesch
Priv.-D
Oberär
Frau D
Frau P
Dr. me
Dr. me
Dr. me
Frau D
Hörzer
Ärztlic
Prof. D
Rhinol
Endos
Priv.-D
Funkti
rekons
Frau D
Dr. me
Forsch
Priv.-D
Sprech
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Poliklin
Tel:
Privats
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HNA3:
Poliklin
Webse

ANNEX B. ETHICS COMMITTEES APPROVALS

The clinical study approvals have been acquired for retrospective and prospective studies in the following participating hospitals:

BD2Decide Hospital	Retrospective study	Prospective study
AOP	Ethics Committee Parma 12/04/2016. Resolution n. 7/16 Prot. n. 12532 08/0472016	Ethics Committee Parma 12/04/2016. Resolution n. 7/16 Prot. n. 12534 08/0472016
INT	Ethics Committee Istituto Nazionale dei Tumori Milano, 22/03/2016. Study N. INT 66/16	Ethics Committee Istituto Nazionale dei Tumori Milano, 22/03/2016. Study N. INT 65/16
UDUS	Included in Ethics Committee Düsseldorf 22/04/2016 and 11.07.2016 Resolution n. RH/NM 2016-09 UDUS Nr. 5591 and 5472	Ethics Committee Dusseldorf 22/04/2016. Resolution n. RH/NM 2016-09; UDUS-Nr. 5472
MAASTRO	Outcome Prediction in Head&Neck Cancer Patients After Radiotherapy Patients (OutcomeH&N), ClinicalTrials.gov Identifier: NCT01985984 The Head and Neck Tumor Biobank, ClinicalTrials.gov Identifier: NCT01644786	Ethics Committee Maastro 03/05/2016. Resolution n. 5472
VUmc	Not required, already achieved for previous studies according to National Ethics Regulations	Not applicable. VUmc does not perform prospective study.

AOP

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Parma

Comitato Etico per Parma

Il Comitato Etico per Parma in data 12 Aprile 2016 verbale n. 7/16

ha valutato il seguente studio osservazionale

A prospective Observational Study for the Development and Validation of New Prognostic Models in Head and Neck Cancer Patients for Decision Support.

PROTOCOLLO: BD2DecidePro nell'ambito del Progetto **"Big data and models for personalized Head and Neck Cancer Decision Support".**
SPONSOR/PROMOTORE: HORIZON 2020
INVESTIGATORE PRINCIPALE: Prof. Tito Poli U.O. Chirurgia Maxillo-Facciale
DOCUMENTI ESAMINATI:

- Lettera di trasmissione
- Protocollo, Protocol Version 2.1 – 01 March 2016
- Sinossi, Versione 2.1 del 01 Marzo 2016
- Grant Agreement
- Scheda Clinica per la Raccolta dei Dati, Version 1.1 – 27 November 2015
- Allegato B3 – Dichiarazione del Promotore – Sperimentazione NO PROFIT, Versione del 18/03/2016
- Notifica raccolta dati retrospettivi, 18/03/2016
- Delega ai collaboratori, 21/03/2016
- Elenco Centri partecipanti ed Elenco Centri collaboratori, Versione 1 del 18/03/2016
- Foglio Informativo e dichiarazione di consenso alla sperimentazione nel caso di pazienti adulti e capaci, Versione 1 del 18/03/2016
- Foglio Informativo e dichiarazione di consenso alla sperimentazione nel caso di soggetti incapaci, Versione 1 del 18/03/2016
- Informativa e manifestazione del consenso al trattamento dei dati personali, Versione 1 del 18/03/2016
- Informativa e manifestazione del consenso al trattamento dei dati personali pazienti incapaci, Versione 1 del 18/03/2016
- Lettera al Medico Curante, Versione 1 del 18/03/2016
- Curriculum Vitae Prof. Poli
- Modulo Assunzione di Responsabilità e assenza di conflitto di interessi per STUDIO NO-PROFIT, versione del 18/03/2016
- Parere del Centro Coordinatore

Comitato Etico per Parma
Via Gramsci, 14 - 43100 Parma
T. +39.0521.703013-703957- F. +39.0521.704702
comitatoetico@ao.pr.it - www.ao.pr.it/comitatoetico

UNIVERSITÀ DEGLI STUDI DI PARMA

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Ospedaliero - Universitaria di Parma

SERVIZIO SANITARIO REGIONALE
EMILIA-ROMAGNA
Azienda Unità Sanitaria Locale di Parma

Comitato Etico per Parma

Il Comitato Etico per Parma in data 12 Aprile 2016 verbale n. 7/16

ha valutato il seguente studio osservazionale

A retrospective Observational Study for the Development and Validation of New Prognostic Models in Head and Neck Cancer Patients for Decision Support.

PROTOCOLLO: BD2DecideRe nell'ambito del Progetto **"Big data and models for personalized Head and Neck Cancer Decision Support"**
SPONSOR/PROMOTORE: HORIZON 2020
INVESTIGATORE PRINCIPALE: Prof. Tito Poli U.O. Chirurgia Maxillo-Facciale
DOCUMENTI ESAMINATI:

- Lettera di trasmissione
- Protocollo, Protocol Version 2.1 – 01 March 2016
- Sinossi, Versione 2.1 del 01 Marzo 2016
- Grant Agreement
- Scheda Clinica per la Raccolta dei Dati, Version 1.1 – 27 November 2015
- Allegato B3 – Dichiarazione del Promotore – Sperimentazione NO PROFIT, Versione del 18/03/2016
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- Foglio Informativo e dichiarazione di consenso alla sperimentazione nel caso di soggetti incapaci, Versione 1 del 18/03/2016
- Informativa e manifestazione del consenso al trattamento dei dati personali, Versione 1 del 18/03/2016
- Informativa e manifestazione del consenso al trattamento dei dati personali pazienti incapaci, Versione 1 del 18/03/2016
- Lettera al Medico Curante, Versione 1 del 18/03/2016
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- Parere del Centro Coordinatore

INT

Fondazione I.R.C.C.S.
ISTITUTO NAZIONALE DEI TUMORI

20133 Milano (Italy), Via Venezian, 1 – E-mail: etico@istitutotumori.mi.it – fax: +39 02 2390 3453 – tel.: +39 02 2390 2546

COMITATO ETICO

Dott.ssa Lisa Licitra
S.C. Oncologia Medica 3
Sede

DI - 3370503 - 23/03/2016
Fondazione IRCCS Istituto Nazionale Tumori - Milano
SR: DSCCE

Milano, 22 marzo 2016

Oggetto: *"Studio osservazionale prospettico per lo sviluppo e la validazione di nuovi modelli prognostici in pazienti con tumore della testa e del collo al fine di sviluppare uno strumento di supporto decisionale - BD2DecidePro"*

Con riferimento allo studio osservazionale in oggetto, si comunica che durante la seduta del 22 marzo 2016 il CE ha preso visione della documentazione presentata in data 02 marzo 2016 e informa che, per quanto di sua competenza, nulla osta alla effettuazione dello studio.
A questo studio l'ufficio di segreteria ha assegnato il **N. INT 65/16**. A questo numero ufficiale va fatto riferimento per ogni corrispondenza.

Il Presidente
per Dott. Valter Torri

DR. R. LABIANCA

Fondazione I.R.C.C.S.
ISTITUTO NAZIONALE DEI TUMORI

20133 Milano (Italy), Via Venezian, 1 – E-mail: etico@istitutotumori.mi.it – fax: +39 02 2390 3453 – tel.: +39 02 2390 2546

COMITATO ETICO

Dott.ssa Lisa Licitra
S.C. Oncologia Medica 3
Sede

DI - 3370506 - 23/03/2016
Fondazione IRCCS Istituto Nazionale Tumori - Milano
SR: DSCCE

Milano, 22 marzo 2016

Oggetto: *"Studio osservazionale retrospettivo per lo sviluppo e la validazione di nuovi modelli prognostici in pazienti con tumore della testa e del collo al fine di sviluppare uno strumento di supporto decisionale - BD2DecideRe"*

Con riferimento allo studio osservazionale in oggetto, si comunica che durante la seduta del 22 marzo 2016 il CE ha preso visione della documentazione presentata in data 02 marzo 2016 e informa che, per quanto di sua competenza, nulla osta alla effettuazione dello studio.
A questo studio l'ufficio di segreteria ha assegnato il **N. INT 66/16**. A questo numero ufficiale va fatto riferimento per ogni corrispondenza.

Il Presidente
Dott. Valter Torri

DR. R. LABIANCA

UDUS

Medizinische Fakultät
Ethikkommission

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

Heinrich-Heine-Universität Düsseldorf ✉ 40204 Düsseldorf

Frau
Dr. med. Kathrin Scheckenbach
Klinik für Hals-Nasen-Ohren-Heilkunde

- HIER -

Prof. Dr. med. T. Hohlfeld
Vorsitzender

Prof. Dr. rer. nat. K.-D. Kröncke
Geschäftsführer

Dr. rer. nat. N. Fitzner
Wissenschaftliche Mitarbeiterin

Telefon 0211 / 81-19591
Telefax 0211 / 81-19592
Ethikkommission@
med.uni-duesseldorf.de

Ethikkommission an der Medizinischen Fakultät der HHU Düsseldorf
Kinderklinik Geb. 13.41
Ebene 03 Raum 34
Moorenstr 5
40225 Düsseldorf

www.uni-duesseldorf.de

Bitte stets angeben:
Interne Studiennummer: 5472
„Software-basiertes Model zur personalisierten Entscheidungsunterstützung bei Kopf-Hals-Karzinompatienten - Big Data and models for personalized Head and Neck Cancer Decision support“

Düsseldorf, 22.04.2016

Sehr geehrte Frau Dr. Scheckenbach,

die Ethikkommission der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf hat das von Ihnen vorgelegte Studienprotokoll mit dem o.g. Titel geprüft und beurteilt.

Seitens der Ethikkommission bestehen keine ethischen oder rechtlichen Bedenken gegen die Durchführung Ihrer Studie.

Nach Abschluss des Projektes bitten wir um Übersendung eines knappen Schlussberichtes oder einer abschließenden Publikation.

Für die Durchführung Ihrer Studie wünschen wir viel Erfolg!

Mit freundlichen Grüßen

i. A. N. Fitzner

Prof. Dr. Klaus-Dietrich Kröncke
i. A. der Kommission

Seite 1 von 1

Medizinische Fakultät
Ethikkommission

HEINRICH HEINE
UNIVERSITÄT DÜSSELDORF

Heinrich-Heine-Universität Düsseldorf ✉ 40204 Düsseldorf

Frau
Dr. med. Kathrin Scheckenbach
Klinik für Hals-Nasen-Ohren-Heilkunde

- HIER -

Prof. Dr. med. T. Hohlfeld
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Wissenschaftliche Mitarbeiterin

Telefon 0211 / 81-19591
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Kinderklinik Geb. 13.41
Ebene 03 Raum 34
Moorenstr. 5
40225 Düsseldorf

www.uni-duesseldorf.de

Düsseldorf, 11.07.2016

Bitte stets angeben:
Interne Studiennummer: 5591
„Retrospektive Evaluation von multimodalen Outcome-Indikatoren bei Patienten mit Tumorerkrankungen im Kopf-Hals-Bereich“

Sehr geehrte Frau Dr. Scheckenbach,

die Ethikkommission der Medizinischen Fakultät der Heinrich-Heine-Universität Düsseldorf hat das von Ihnen vorgelegte Studienprotokoll mit dem o.g. Titel geprüft und beurteilt.

Seitens der Ethikkommission bestehen keine ethischen oder rechtlichen Bedenken gegen die Durchführung Ihrer retrospektiven pseudonymisierten Datenanalyse.

Nach Abschluss des Projektes bitten wir um Übersendung eines knappen Schlussberichtes oder einer abschließenden Publikation.

Für die Durchführung Ihrer retrospektiven pseudonymisierten Datenanalyse wünschen wir viel Erfolg!

Mit freundlichen Grüßen

i. A. N. Fitzner

Prof. Dr. Klaus-Dietrich Kröncke
i. A. der Kommission

Seite 1 von 1

MAASTRO

Aan de directie van
MAASTRO CLINIC

Maastricht, 3 mei 2016
RH/NM 2016-09

Geachte directie,

De Institutional Review Board heeft in haar vergadering van 6 april 2016 een Positief advies gegeven voor deelname aan de studie: Retrospective Observational Study for the Development and Validation of New Prognostic Models in Head and Neck Cancer Patients:BD2DecideRe. LOKAAL: 15-52-16/12-extern.

- De studie is niet-WMO plichtig.
- De financiële middelen voor deze studie worden gefinancierd uit de 3e geldstroom
- De patiënt ontvangt geen financiële tegemoetkoming.
- De logistieke invulling is geregeld.
- Aanmelden van de studie bij het Patiëntveiligheidsteam is niet nodig.

Het protocol (versie V1.1 van 27 november 2015) en de begroting zijn in te zien in Topdesk onder nummer W 16 02 00050.

De verantwoordelijke budgethouder/financieel verantwoordelijke is Philippe Lambin.

De onderzoeker is verantwoordelijk voor het goede verloop van deze studie. We rekenen op een regelmatige jaarlijkse terugrapportage aan de IRB en indien nodig aan de directie.

We gaan ervan uit dat de onderzoeker GCP gecertificeerd is en op de hoogte is van de wetgeving, de verantwoordelijkheden en de verplichtingen.

Wij stellen het op prijs dat deze studie wordt afgerond bij voorkeur met een peer-reviewed publicatie.

Met vriendelijke groet,

E-mail: info@maastro.nl
Dr. Tanslaan 12
6229 ET MAASTRICHT
T: +31 (0)88 44 55 666
F: +31 (0)88 44 55 667
Postbus 5800
6202 AZ MAASTRICHT

Prof. dr. Ph. Lambin
Voorzitter Institutional Review Board
MAASTRO CLINIC

m.a.a.
dr. F. Hoebers (coördinator)
Dr. K. Smits (hoofd datamanagement)
Secretariaat RvB

academisch ziekenhuis
Maastricht

P. Debyelaan 25
postbus 5800
6202 AZ Maastricht

telefoon 043-387 65 43
telefax 043-387 78 78

academisch ziekenhuis
Maastricht
azM

C. Offermann, MA
Sr. Datamanager
MAASTRO clinic

afdeling METC azM/UM
uw kenmerk
ons kenmerk METC 12-4-004.6/ivb
doorkiesnummer 043-387 6009
datum 27 maart 2012

secretariaat.metc@mumc.nl
www.azm.nl/info/azMorganisatie/MEC

Betreft: Positief advies niet-WMO / METC 12-4-004
Storage of head and neck tumor samples in a biobank for future genomic-based research aiming at improved outcome prediction: "The head and neck tumor biobank"

Geachte mevrouw Offermann,

De medisch-ethische toetsingscommissie (METC) azM/UM heeft bovengenoemd onderzoeksvoorstel besproken in haar vergaderingen van 01-02-2012 en 14-03-2012.

Geconcludeerd is dat het geen onderzoek in het kader van de Wet medisch-wetenschappelijk onderzoek met mensen (WMO) betreft. De METC azM/UM heeft geen bezwaar tegen de uitvoering van bovengenoemd onderzoeksvoorstel en brengt derhalve een positief advies uit.

De commissie heeft de volgende stukken in haar toetsing betrokken:
- de aanbiedingsbrief d.d. 13-01-2012;
- de nadere toelichtingen d.d. 12-03-2012 en 19-03-2012;
- het protocol versie 5.0 d.d. 15-03-2012.

De commissie ontvangt nog graag bericht van de start- en einddatum van genoemde studie.

De commissie wijst u erop dat het onderzoek pas gestart mag worden na ontvangst van een goedkeuringsbesluit van de Raad van Bestuur van het Maastricht UMC+.

Met vriendelijke groet, namens de METC azM/UM,

mr. R.C.W. van Gils, ambtelijk secretaris

Cc.: Clinical Trial Center Maastricht
Dr. F.J.P. Hoebers, MAASTRO clinic

VUmc

commissie

De Boelelaan 1117 postbus 7057 telefoon 020 444 4444 www.VUmc.nl
1081 HV Amsterdam 1007 MB Amsterdam

Medisch EthischeToetsingscommissie
VU medisch centrum
voorzitter: Prof. dr. P.E. Postmus
postadres secretaris: 6 Z 202

Dr. B.J.M. Braakhuis
Afdeling KNO
Kamer 1D 116

VU medisch centrum

onderwerp
positief oordeel

datum
12 juni 2008

NL22230.029.08

ons kenmerk
2008/71

doorkiesnummer
(020) 44 43488
fax 020 44 43566
email subcom-ethiek.org@vumc.nl

Geachte heer Braakhuis,

De Medisch Ethische Toetsingscommissie Vrije Universiteit medisch centrum (bevoegd tot oordelen op grond van WMO art. 2.2.a) oordeelt thans in positieve zin omtrent de uitvoering van het onderzoek met titel:

Improving the diagnosis and treatment of patients with head and neck squamous cell carcinoma: collection of tumor tissues, the 'HNcol' study

Aanvrager van het onderzoek: Dr. B.J.M. Braakhuis
Verrichter: VUmc te Amsterdam
METc VUmc registratienummer: 2008/71

Vergadering en documenten
De goedkeuring, waartoe in principe besloten is in de vergadering van 15-5-2008, is gebaseerd op de volgende documenten:
- protocol d.d. 27-5-2008
- patiënteninformatiebrief d.d. 23-5-2008
- toestemmingsverklaring d.d. 1-3-2008
- begeleidende brief d.d. 13-3-2008
- begrotingsverklaring d.d. 13-3-2008
- CV hoofdonderzoeker (Braakhuis)
- CV onafhankelijk arts (Bodegraven)
- goedkeuring CWO d.d. 19-2-2008
- print ABR aanvraagformulier versie 2 d.d. 27-5-2008
- privacyreglement VUmc d.d. 13-3-2008
- verzekeringscertificaat Centramed d.d. januari 2007
- bewijs dekking aansprakelijkheid Centramed t.b.v. VUmc d.d. oktober 2007

Motivering
De commissie is van oordeel dat het onderzoek voldoet aan het bepaalde in de van toepassing zijnde wet- en regelgeving, met name de WMO en, voorzover relevant, het ICH/GCP richtsnoer.

U dient zich te realiseren dat in de nabije toekomst regels betreffende biobanking aangescherpt kunnen worden.

04.001.98 / 1

Verzekering
De METc VUmc heeft vastgesteld dat op correcte wijze uitvoering is gegeven aan de verzekeringsplicht in artikel 7 van de WMO, zoals uitgewerkt in het Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen. Naar het oordeel van de commissie gaat het onderzoek gepaard met risico.

Verplichtingen
De commissie verwacht dat
- de startdatum van het onderzoek de commissie ter kennis zal worden gebracht
- elke onverwachte bijwerking die zich tijdens het onderzoek voordoet bij de proefpersonen onverwijld aan de commissie gemeld wordt, voorzien van een toelichting betreffende de consequenties voor het onderzoek
- veranderingen in het onderzoeksprotocol aan de commissie worden voorgelegd, voorzien van een toelichting betreffende de consequenties voor de proefpersonen
- jaarlijks een rapport over de voortgang van het onderzoek aan de commissie zal worden toegestuurd
- de beëindiging van het onderzoek, hetzij omdat het onderzoek voltooid is hetzij om andere redenen, de commissie ter kennis zal worden gebracht
- de resultaten van het onderzoek aan de commissie zullen worden gemeld

De commissie heeft de bevoegdheid haar positieve oordeel in te trekken als vaststaat dat de uitvoering van het onderzoek ernstig tekort schiet.
Het voorliggend oordeel verliest zijn geldigheid indien de start van het onderzoek niet binnen 1 jaar plaatsvindt.

Volledigheidshalve maken wij u er op attent dat het onderzoek pas mag worden uitgevoerd nadat u schriftelijk toestemming hebt gekregen van (het plv hoofd Bureau Medische Zaken namens) de raad van bestuur.

Administratief beroep
Tot slot wijzen wij u erop, dat op grond van artikel 23 van de Wet medisch-wetenschappelijk onderzoek met mensen, degene wiens belang rechtstreeks bij een besluit is betrokken daartegen binnen zes weken na de dag waarop het besluit bekend is gemaakt, een administratief beroepschrift kan indienen bij de Centrale Commissie Mensgebonden onderzoek. Een dergelijk administratief beroepschrift dient u te adresseren aan: CCMO, Postbus 16302, 2500 BH Den Haag.

Met vriendelijke groet,
namens de Medisch Ethische Toetsingscommissie,

prof. dr. P.E. Postmus, voorzitter

dr. P. de Haan, secretaris

c.c.: Centrale Commissie Mensgebonden Onderzoek te Den Haag (CCMO), **NL22230.029.08** - *digitale verzending*

Samenstelling commissie

prof. dr. P.E. Postmus	voorzitter, longarts	dr. D. De Jong	chirurg
mw. M. Baak	verpleegkundige	dr. J. Killestein	neuroloog
mw. dr. B. van Baarsen en dr. M.J.P.A. Janssens	medisch ethici	dr. M. Klein	neuropsycholoog
dr. ir. P.D. Bezemer	klinisch epidemioloog	dr. M.C.J. Kneyber	kinderintensivist
mw. dr. C. Boer	biomedicus	mw. P. Roodenberg	lekenlid
mr. F.J. Faber en mw. mr. A.J.G.M. Janssen	juristen	mw. dr. A.I. Veldkamp en drs. A.J. Wilhelm	ziekenhuisapothekers-klinisch farmacologen
dr. K. Hoekman	internist-oncoloog	prof. dr. F.J.H. Tilders	farmacoloog

VU medisch centrum

raad van bestuur

De Boelelaan 1117 postbus 7057 telefoon 020 444 4444 www.VUmc.nl
1081 HV Amsterdam 1007 MB Amsterdam fax 020 444 3564

Dr. B.J.M. Braakhuis
Afdeling KNO
Kamer 1D 116

VU medisch centrum

datum
12 juni 2008

onderwerp
onderzoeksprotocol

ons kenmerk
2008/71

doorkiesnummer
(020) 44 43555

Geachte heer Braakhuis,

Mede op grond van het positieve advies van de Medisch Ethische Toetsingscommissie Vrije Universiteit medisch centrum verleen ik hierbij mijn goedkeuring aan de uitvoering van het onderzoek volgens het protocol met titel:

"Improving the diagnosis and treatment of patients with head and neck squamous cell carcinoma: collection of tumor tissues, the 'HNcol' study"

Ik neem aan dat uwerzijds ter zake van dit onderzoek het nodige overleg wordt gepleegd met de overige betrokken ziekenhuisdisciplines.

Indien er sprake is van gezonde proefpersonen en/of patiënten die elders onder behandeling zijn maar hier in het onderzoek worden opgenomen, dienen deze op gelijke wijze als patiënten van ons ziekenhuis te worden geregistreerd.
Vervolgens kan door middel van de vermelding van 'researchpatiënt' met de BIZA worden afgesproken dat deze patiënt geen rekening zal ontvangen.

Met collegiale hoogachting,
namens de raad van bestuur VUmc

dr. J.C. Roos, nucleair geneeskundige n.p.
plaatsvervangend hoofd instituut ondersteuning patiëntenzorg

kopie aan:
afdelingshoofd
hoofd afdeling apotheek
hoofd afdeling klinische chemie
manager bedrijfsvoering

04.002.21 / 1

commissie

De Boelelaan 1117 postbus 7057 telefoon 020 444 4444 www.VUmc.nl
1081 HV Amsterdam 1007 MB Amsterdam

Medisch Ethische Toetsingscommissie
VU medisch centrum
voorzitter: prof. dr. J.A. Rauwerda
intern postadres: BS7, kamer H-565
telefoon: 020 - 44 45555
e-mail: metc@vumc.nl
website: www.vumc.nl/metc

prof.dr. R. H. Brakenhoff
Afdeling KNO
ZH 1D 116

VUmc

onderwerp	ons kenmerk	datum
positief nader oordeel	2008.071 (A2016.035) NL22230.029.08	9 februari 2016

Geachte heer Brakenhoff,

De Medisch Ethische Toetsingscommissie VU medisch centrum (bevoegd tot oordelen op grond van WMO art. 2.2.a) bevestigt de ontvangst van het amendement bij het protocol met ons kenmerk 2008.071 met titel

Improving the diagnosis and treatment of patients with head and neck squamous cell carcinoma: collection of tumor tissues, the 'HNcol' study

Het ingediende amendement brengt, na toetsing aan artikel 3 van de WMO, geen verandering in de goedkeuring die aan dit onderzoek eerder werd verleend.

De goedkeuring van het amendement, dat besproken is op 09/02/2016, is gebaseerd op de volgende documenten:

Sectie	Onderwerp	Versie
A1	aanbiedingsbrief	d.d. 20-1-2016
B1	ABR-formulier	versie 4 d.d. 20-1-2016
C1	onderzoeksprotocol	clean d.d. 19-1-2016
C1	onderzoeksprotocol	track changes d.d. 19-1-2016
E12	informatiebrief incl. toestemmingsverklaring	track changes versie 4 d.d. 19-1-2016
E12	informatiebrief incl. toestemmingsverklaring	versie 4 d.d. 15-1-2016
I31	CV hoofdonderzoeker	R.H. Brakenhoff

Beroepsprocedure
Tegen dit besluit kan een belanghebbende op grond van artikel 23 van de WMO binnen zes weken na de dag waarop het besluit is bekend gemaakt, administratief beroep instellen bij de Centrale Commissie Mensgebonden Onderzoek (CCMO). Het beroepschrift dient u te adresseren aan: CCMO, Postbus 16302, 2500 BH Den Haag.

Met vriendelijke groet,
namens de METc VUmc,

Mevr. dr. L. Schoo, secretaris

bijlage(n): samenvatting amendement

c.c.: Centrale Commissie Mensgebonden Onderzoek te Den Haag (CCMO) - *digitaal uploaden*

Positief nader oordeel METc VUmc 2008.071/NL22230.029.08

VUmc

Samenvatting amendement

Verandering van coordinerend onderzoeker/projectleider

Samenstelling METc VUmc

prof. dr. J.A. Rauwerda	voorzitter, chirurg
prof. dr. M.A. Blankenstein	plv. voorzitter, klinisch chemicus
drs. P.M. Bet	ziekenhuisapotheker-klinisch farmacoloog (plv.)
mevr. prof. dr. C. Boer	biomedicus
mevr. dr. M.A. Bremmer	psychiater
mevr. drs. M.M.E. van Dijk	verpleegkundige
dr. B. Drukarch	arts-farmacoloog
mr. F.J. Faber	jurist
dr. ir. ing. Th.J.C. Faes	klinisch fysicus (plv.)
dr. M.J.J. Finken	kinderarts (plv.)
dr. E.G. Haarman	kinderarts
dr. R. Houtepen	medisch ethicus (plv.)
dr. M.J.P.A. Janssens	medisch ethicus
dr. M. Klein	neuropsycholoog
mevr. dr. M. Kouwenhoven	neuroloog (plv.)
dr. M.D. Lagerweij	tandarts
Mevr. L. Muter	proefpersonenlid (plv.)
mevr. G. Nijman	proefpersonenlid
dr. B.W. van Oosten	neuroloog
mevr. dr. A.F.W. van der Steeg	chirurg
mevr. dr. C.B. Terwee	methodoloog (plv.)
mevr. dr. E.A. te Velde	chirurg
mevr. dr. N. Veldhuijzen	methodoloog (plv.)
dr. ir. P. van de Ven	methodoloog
prof. dr. ir. R. Verdaasdonk	klinisch fysicus
ing. S.W. Vianen	stralingsdeskundige
mevr. dr. C. Widdershoven	medisch ethicus (plv.)
drs. A.J. Wilhelm	ziekenhuisapotheker-klinisch farmacoloog

Positief nader oordeel METc VUmc 2008.071/NL22230.029.08

VUmc

ANNEX C. REGISTRATION OF BD2DECIDE CLINICAL STUDY

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Search for studies:

Now Available: Final Rule for FDAAA 801 and NIH Policy on Clinical Trial Reporting

Find Studies | About Clinical Studies | Submit Studies | Resources | About This Site

Home > Find Studies > Study Record Detail

Big Data and Models for Personalized Head and Neck Cancer Decision Support (BD2Decide) (BD2Decide)

This study is currently recruiting participants. (see Contacts and Locations)

Verified July 2016 by Azienda Ospedaliero-Universitaria di Parma

Sponsor:
Azienda Ospedaliero-Universitaria di Parma

Collaborators:
Fondazione IRCCS Istituto Nazionale dei Tumori, Milano
VU University Medical Center
Heinrich-Heine University, Duesseldorf
Maastricht Radiation Oncology
Istituto Superiore di Sanità

Information provided by (Responsible Party):
Tito Poli, Azienda Ospedaliero-Universitaria di Parma

ClinicalTrials.gov Identifier:
NCT02832102

First received: June 1, 2016
Last updated: July 11, 2016
Last verified: July 2016
History of Changes

Full Text View | Tabular View | No Study Results Posted | Disclaimer | How to Read a Study Record

ANNEX D SOPS

SOP for genetic materials provision

IMPLEMENTING LETTER

This document must be attached to each transfer of materials.

Fondazione IRCCS Istituto Nazionale dei Tumori
Mr. Loris De Cecco
Loris De Cecco, unit Experimental Oncology and Molecular Medicine
Via Venezian, 1
20133 Milano - Italy

Transfer of Biological material for BD2Decide project.

Tissue Management SOPs for Genomics analysis at INT

Please find enclosed:

N. <insert n.> of the following samples:

Type of sample	Procedure: Indicate the timing and type of sample (primary surgery, surgery after RT, biopsy, …)	Storage	Shipping condition
Cut sections from FFPE blocks	**Macrodissected areas from 6-8 sections of 8mm in a screw-cap tube, corresponding to 3 mm^3** Macrodissection of the tumor areas is required, avoiding stroma and necrotic areas, should be performed by an experienced pathologist in each site of accrual. Tumor content should be 80%, otherwise the sample has to be recorded with the actual tumor content.	The tubes should be stored at 4ºC	The tubes should be sent at 4ºC
Biopsies	**Macrodissected areas from 3-5 sections of 8mm in a screw-cap tube,** Macrodissection of the tumor areas is required, avoiding stroma and necrotic areas, should be performed by an experienced pathologist in each site of accrual. Tumor content should be 80%, otherwise the sample has to be recorded with the actual tumor content.		

Packaging Instruction

TS samples should be packaged in order to comply with IATA regulations (see http://www.iata.org for further information).

All TS samples, independent of their infectious characteristics, should always follow a triple packaging system:

1) Properly labeled, outer rigid packaging with minimal dimensions.
2) Watertight, secondary packaging with absorbent material (shocks and/or leaks)
3) Watertight inner packaging [e.g. the blood collection tube(s), cryovial(s)]

National authorities (country of origin/destination) and courier companies have the possibility to incorporate stricter exceptions on the IATA general rules.

Contact person	Dr. Loris De Cecco
Full address to which samples for the genomics study should be sent	Fondazione IRCCS Istituto Nazionale dei Tumori Dipartimento di Oncologia Sperimentale e Medicina Molecolare, Genomica Funzionale Via Amadeo 42, 20133 Milano, Italy Phone: *+39(0)223905130* *Fax: +39(0)2 2390 2764* E-mail: loris.dececco@istitutotumori.mi.it

For and behalf of the PROVIDING PARTNER	**For and behalf of the RECEIVING PARTNER**
Providing partner PI Title: SIGNATURE STAMP OF ORGANIZATION Date:	Fondazione IRCCS Istituto Nazionale dei Tumori Mr. Enzo Lucchini Title: President SIGNATURE Date:

LAB MANUAL FOR PROCESSING OF THE TISSUE SAMPLES (TS) FOR THE GENOMICS BIOMARKER STUDY

Steps	Procedure:	Output	Storage	sharing
Nucleic acid extraction	RNA extraction will be performed using the RNeasy FFPE Kit (Qiagen) and automated using Qiacube Station following manufacture's protocols.	RNA	Aliquots will be identified using TwinElix device and tubes will be stored in alarmed fridge at -80°C	left-overs will be sent back to the sites, if requested
Quality check	quantity and quality controls of nucleic acids will be performed by Agilent TapeStation	document	pdf file archived in INT internal server	If needed
Library construction	Sequencing libraries for whole-transcriptome analysis will be prepared from total RNA with the TruSeq RNA Access Library Prep Kit (Illumina Inc., San Diego, CA), specifically designed for RNA isolated from FFPE tissue. Briefly, 10-200 ng of total RNA will be reverse transcribed to generate blunt-end ds cDNA followed by adapter ligation and amplification. After quality control check, the cDNA library templates will be enriched in the targeted region of interest with the capture probes.	cDNA with adapters and barcodes	Aliquots will be identified using TwinElix device and tubes will be stored in alarmed fridge at -20°C	After sequencing and data quality check, the left-over will be discarded
Sequencing,	The enriched pooled libraries	FastQ	FastQC file	No sharing

quality control and primary data generation	will be sequenced on llumina NextSeq™500 sequencer using NextSeq500 kit and SBSv2 sequencing reagents. Transcriptome data generated on the NextSeq 500 System will be analysed in BaseSpace and FastQ will be generated through FastQC .		will be given to each center for long term storing	
Secondary data	Subsequently, the reads will be aligned to a reference genome (hg19, GRCh37) using TopHat 2 to generate a BAM file which can be used in subsequent stages of analysis.	BAM file	The BAM file will be given to each center for long term storing	No sharing
Tertiary data	Expression data for each gene will be summarized as reads per kilobase of exon per million reads mapped (RPKM)	Txt file		Expression data will be shared among the consortium

FFPE= Formalin-fixed paraffin-embedded

BAM= Binary compressed SAM format

RPKM= reads per kilobase of transcript per million reads mapped

SOP for HPV testing provision

IMPLEMENTING LETTER

This document must be attached to each transfer of materials.

VU medical center, part of Foundation VUmc
Prof RH Brakenhoff
unit Dept Otolaryngology-Head and Neck Surgery
De Boelelaan 1117, 1081 HV Amsterdam, The Netherlands

Transfer of Biological material for BD2Decide project.

Please find enclosed:

N. <insert n.> of slides of tumor biopsies/tumor specimens.

MATERIALS TO BE SENT TO VUMC

Type of sample	**Procedure: Indicate the timing and type of sample (primary surgery, surgery after RT, biopsy, …)**	**Storage**	**Shipping condition**
Oropharyngeal cancer Cut sections from FFPE blocks	3-5 sections of 5 µm on a water-cleaned microtome with new blade, and mounted on Superfrost Plus microscopic glass slides and dried overnight and labeled “pre1” 2-20 sections of 10 µm are prepared and collected in Sarsted microcentrifuge vial with screw cap Subsequently 2-5 sections of 5 µm are prepared and labeled “after1”	Room temperature	Room temperature

Packaging instruction

TS samples should be packaged in order to comply with IATA regulations (see http://www.iata.org **for further information).**

All TS samples, independent of their infectious characteristics, should always follow a triple packaging system:

1) Properly labeled, outer rigid packaging with minimal dimensions.
2) Watertight, secondary packaging with absorbent material (shocks and/or leaks)
3) Watertight inner packaging [e.g. the blood collection tube(s), cryovial(s)]

National authorities (country of origin/destination) and courier companies have the possibility to incorporate stricter exceptions on the IATA general rules.

Contact persons	RH Brakenhoff
full address to which samples for the HPV study should be sent	RH Brakenhoff Dept Otolaryngology/Head and Neck Surgery, rm ZH 1 D 116 De Boelelaan 1117 1081 HV Amsterdam The Netherlands rh.brakenhoff@vumc.nl, +31-(0)-20-444 40953

For and behalf of the PROVIDING PARTNER	**For and behalf of the RECEIVING PARTNER**
Providing partner PI Title: SIGNATURE Date:	VU medical center drs. C. van der Meulen Title: Managing Director Division II SIGNATURE Date:

Tissue protocol

SAMPLING FOR HPV TESTING

Background

HPV is a major prognostic factor in oropharyngeal cancer. It should be determined by a validated assay, and this is a problem as most assays are not properly validated, particularly applicable for formalin-fixed paraffin-embedded (FFPE) specimen. One well-validated test for FFPWE material is the algorithm previously developed at VUmc that consist of p16 immunostaining followed by a HPV DNA assay. The p16 immunostaining ia automated using the CINTEC kit and a staining is considered positive when more than 70% of the tumor is immunostained for p16. In case of doubt the sample is tested for HPV nucleic acids.

We agreed that the HPV data of all centers that test oropharyngeal cancer for HPV using a combination of p16 immunostaining and a HPV nucleic acid assay is considered reliable. P16 immunostaining only is not acceptable.

The importance of HPV status for non-oropharyngeal cancers has not been studied in enough detail. We will study the role of HPV in oral cancer within BD2. Of note, this will be done ONLY after a DIRECT REQUEST from VUmc to any other partner, hence not standard.

Oropharyngeal cancers:

- Cut sections from FFPE blocks:
  - 2 sections of 3-5 µm are cut on a water-cleaned microtome with new blade, and mounted on Superfrost Plus microscopic glass slides and dried overnight and labeled "pre1"/"pre2" and patient ID.
  - 2-20 sections of 10 µm are prepared and collected in Sarsted microcentrifuge vial with screw cap, and labeled with patient ID. Total tissue area collected should be 1 cm2 of 10 µm.
  - Subsequently 2 sections of 3-5 µm are prepared and labeled "aft1"/"aft2" and patient ID.
- Storage condition: room temperature
- Shipping condition: room temperature
- Shipping to Amsterdam for further processing as follows:
  - H&E staining
  - P16 immunostaining
  - HPV-DNA detection by HPV-Risk Assay (Hesselink et al. JCM 2014), followed by RT-PCR for R6*l transcripts when necessary.

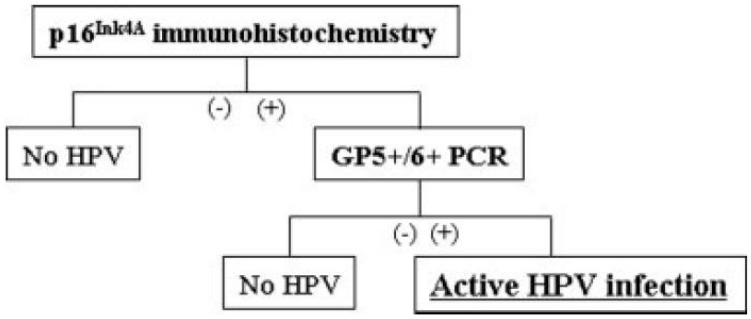

FIGURE 4 – Proposed flowchart for high throughput identification of HNSCC with a clinically relevant HPV infection on paraffin-embedded tissue sections with 100% sensitivity and specificity.

Non-oropharyngeal (oral) cancers:

Punch biopsies of 1 mm will be taken from the tumor block using a KAI dermal punch with plunger and ejected in an Sarsted microcentrifuge vial with screw cap.

- Collect the H&E for routine diagnosis and the FFPE block.
- Check the H&E of the routine diagnosis, and determine the best location for the biopsy
- Estimate the tumor percentage of the area that will be biopsied.
- Determine the right area on the block and take the punch.

- Storage condition: room temperature
- Shipping condition: room temperature
- Shipping to Amsterdam for further processing:
    - H&E staining
    - HPV-detection:

ANNEX E. MTA AND DTA TERMS AND CONDITIONS

MTA TERMS AND CONDITION

II. Terms and Conditions of this Agreement:

1. The PROVIDING PARTNER retains custodianship of the MATERIAL, including any MATERIAL contained or incorporated in MODIFICATIONS. PROVIDING PARTNER acquired the MATERIAL from its patients in accordance with all applicable laws and regulations, including but not limited the Informed Consent of the patient ("Informed Consent").

2. The RECEIVING PARTNER agrees that the MATERIAL:

(a) is to be used soley in accordance with the protocol attached as Annex I ("Protocol");

(b) is to be used solely for teaching and academic or other NONCOMMERCIAL internal research purposes and for the scope of the BD2Decide project;

(c) is to be used only at the RECEIVING PARTNER organization and only in the RECEIVING PARTNER SCIENTIST's laboratory under the direction of the RECEIVING PARTNER SCIENTIST or others working under his/her direct supervision;

(d) will not be transferred to anyone else within the RECEIVING PARTNER organization without the prior written consent of the PROVIDING PARTNER.

(e) will not be disclosed to a THIRD PARTY. RECEIVING PARTNER shall not carry out the RESEARCH PLAN with any THIRD PARTY or entity without the prior written consent of the PROVIDING PARTNER

(f) will be used only in compliance with applicable EU treaties, laws and regulations, as they are amended from time to time, and only after securing related reviews and approvals as such amended treaties, laws and regulations require;

(g) will be used in compliance with the review procedures and ethical guidelines of theBD2Decide Clinical Study Protocol or, where those are superseded by authoritative, higher national standards, in substantial compliance with such standards.;

3. The Material will be transferred with an univocal reference code, which allows its traceability. Under no circumstances will the personal Data of the patient be provided to RECEIVING PARTNER. RECEIVING PARTNER shall not carry out any procedures with the data (linking, comparison, processing) through which the identity of the patient could be derived.

4 Both Material and associated data are collected in accordance with the informed consent form (ICF) and/or the applicable rules and legislation and the Protocol, where the PROVIDING PARTNER resides,, including but not limited to protection of privacy aspects of the medical and personal data of the patients. RECEIVING PARTNER acknowledges that the patients shall at all times have the right to request the PROVIDING PARTNER to revoke the consent

to their MATERIAL and associated data. In the event a patient files such a request with PROVIDING PARTNER, RECEIVING PARTNER shall – upon first request by PROVIDING PARTNER - promptly destroy the Material and associated data in an approved manner, upon PROVIDING PARTNER's first written request. RECEIVING PARTNER shall confirm the PROVIDING PARTNER in writing of the destruction/deletion or complete return of all such Material and associated Data. The Parties further acknowledge that in case of a finding (an unsought and unsuspected patient related result of the research), RECEIVING PARTNER shall promptly inform PROVIDING PARTNER about such finding.

5. Any MATERIAL delivered pursuant to this Agreement is understood to be experimental in nature. The Parties reciprocally acknowledge and accept that, regardless any declaration or specification relevant to the MATERIAL given in the **"Implementing Letter"**, PROVIDING PARTNER estends no warranty, either express or implied, with respect to the nature and properties of the material, which is made available by PROVIDING PARTNER "as is", or that the use of the MATERIAL will not infringe any patent, copyright, trademrk or other proprietary rights.

6. Except as provided in this Agreement, no express or implied licenses or other rights are provided to RECEIVING PARTNER under any patents, patent applications, trade secrets or other proprietary rights of PROVIDING PARTNER, including any altered forms of MATERIAL made by PROVIDING PARTNER.

(a) RECEIVING PARTNER will keep the PROVIDING PARTNER fully informed of any results arising out from BD2Decide *CLINICAL STUDY* carried out with the MATERIAL.

(b) IPR, inventions and data generated through use of MATERIAL are subject to the rules of Section 8 of the *Consortium Agreement*, according to the effective contribution of each Party.

8. The RECEIVING PARTNER agrees to refer to the PROVIDING PARTNER any request for the MATERIAL from anyone other than those persons working under the RECEIVING SCIENTIST's direct supervision.

To the extent permitted by law, the RECEIVING PARTNER assumes all liability for damages which may arise from its use, storage, disposal or transfer of the MATERIAL. The PROVIDING PARTNER and its directors, researchers, officers and employees will not be liable to the RECEIVING PARTNER for any loss, claim or demand made by the RECEIVING PARTNER, or made against the RECEIVING PARTNER by any other party, due to or arising from the use of the MATERIAL by the RECEIVING PARTNER, except to the extent permitted by law when caused by the gross negligence or willful misconduct of the PROVIDING PARTNER.

9.. This agreement shall not be interpreted to prevent or delay publication of research findings resulting from the use of the MATERIAL.

The dissemination of Results including but not restricted to publications and presentations, shall be governed by Article 29 of the *Grant Agreement* and of Art. 8.3 of the *Consortium Agreement*.

10.. This Agreement will terminate on the earliest of the following dates:

(a) at the end of BD2Decide project as defined in the Grant Agreement and its amendments or
(b) in case of termination of either Party's participation to BD2Decide CLINICAL STUDY or
(c) on completion of the RECEIVING PARTNER's current research with the MATERIAL, or
(d) on thirty (30) days written notice by either Party to the other.

Upon the effective date of termination, or if mutually agreed, any deferred effective date of termination, RECEIVING PARTNER will discontinue its use of the MATERIAL and will, upon direction of the PROVIDING PARTNER, destroy any remaining MATERIAL.

11. The MATERIAL is provided at no cost for the RECEIVING PARTNER.

12. This Agreement shall be governed and enforced in accordance with the laws of Belgium. All disputes arising in connection with this Agreement shall exclusively be submitted to the competent court in Brussels, Belgium.

13. General Terms

For what not expressly set out in this Agreement, the Grant Agreement and Consortium Agreement terms and conditions will apply in relation to transfer of MATERIAL between the Parties.
In case the terms of this Agreement are in conflict with the terms of the Grant Agreement, the terms of the latter shall prevail. In case the terms of this Agreement are in conflict with the terms of the Consortium Agreement, the terms of the latter shall prevail.

Should any provision of this Agreement become invalid, illegal or unenforceable, it shall not affect the validity of the remaining provisions of this Consortium Agreement. In such a case, the Parties concerned will negotiate a valid and practicable provision which fulfils the purpose of the original provision.

IN WITHESS WHEREOF, the Parties have executed this Agreement, in duplicate originals, as of the EFFECTIVE DATE.

AGREED by the parties by their authorised signatories

Place and date Place and date

DTA TERMS AND CONDITIONS

II. Terms and Conditions of this Agreement:

1. The PROVIDING PARTNER is the hoder of DATA and CONFIDENTIAL INFORMATION.

2. The PROVIDING PARTNER grants access to the DATA and CONFIDENTIAL INFORMATION in anonymized/encoded form to the RECEIVING PARTNER and the SCIENTIFIC SCIENTIST for statistical purposes as described in the RESEARCH PLAN defined in the "Annex I - *Description of the Action*, Part A and B" attached to the GA and in the related Study Protocol approved by Ethical Committees of CLINICAL PARTNERS.

3. The RECEIVING PARTNER and the RECEIVING SCIENTIST agree that the DATA:

(h) are to be used solely for NONCOMMERCIAL PURPOSES.

(i) are to be used solely at the RECEIVING PARTNER for the scope of the BD2Decide CLINICAL STUDY as described in the RESEARCH PLAN and/or within the informed consent for the use of DATA provided by participating patients, only in the RECEIVING SCIENTIST's laboratory under the direction of the RECEIVING SCIENTIST or other authorized staff working under his/her direct supervision who have a need to know ("Authorized Users");

(j) will not be transferred to anyone else within the RECEIVING PARTNER organization without the prior written consent of the PROVIDING PARTNER;

(k) will not be disclosed to a THIRD PARTY. RECEIVING PARTNER shall not carry out the RESEARCH PLAN with any THIRD PARTY or entity without the prior written consent of the PROVIDING PARTNER;

(l) will be used only in compliance with applicable EU treaties, laws and regulations, as they are amended from time to time, and only after securing related reviews and approvals as such amended treaties, laws and regulations require;

(m) will be used, in compliance with the review procedures and ethical guidelines of theBD2Decide RESEARCH PLAN and according to the informed consent for the use of personal data provided by participating patients, or, where those are superseded by authoritative, higher national standards, in substantial compliance with such standards.

4. RECEIVING PARTNERS shall procure that its Authorized Users are made aware and will be bound by terms similar to those in this Agreement so that each of the Authorized Users comply with the relevant duties, obligations and restrictions imposed on RECEIVING PARTNERS by this Agreement. Any act or omission of any such Authorized User which, if it had been committed or omitted by a RECEIVING PARTNER would have been a breach to this Agreement and will be deemed to be a breach of this Agreement by that RECEIVING PARTNER.

5. DATA will be collected, treated and provided to the RECEIVING PARTNER by PROVIDING SCIENTIST in a format to be agreed upon in writing by the RECEIVING SCIENTIST and the PROVIDING SCIENTIST, by signing the attached IMPLEMENTING LETTER, in accordance to the decisions taken within the RESEARCH PLAN.

6. Should the RECEIVING PARTNER inadvertently identify any individual donor or Data Subject included in the DATA they will neither record this fact nor share the identification of that individual with any other person, and nor will they attempt to contact the individual themselves.

7. RECEIVING PARTNER will not attempt to contact any of the donors or Subjects included in the DATA supplied.

8. This agreement shall not be interpreted to prevent or delay publication of research findings resulting from the use of the DATA.

   Publications or disclosures using the DATA must include at least one (1) co-author of the PROVIDING PARTNER and at least one (1) co-author of the RECEIVING PARTNER.

9. This Agreement will terminate either

(e) at the end of BD2Decide project as defined in the Grant Agreement, in and its amendments or
(f) in case of termination of either Party's participation to BD2Decide CLINICAL STUDY or
(g) on completion of the RECEIVING PARTNER's current research with the DATA,
(h) or on thirty (30) days written notice by either Party to the Consortium through the Coordinator.

Upon the effective date of termination, or if mutually agreed, any deferred effective date of termination, RECEIVING PARTNER will discontinue its use of the DATA except for the following reasons, in compliance with EU and National laws:

(a) statistical purposes and documentation for peer-reviewed publications, also with the support pof RECEIVING PARTRERS
(b) submission of patents or other IPR protection registration
(c) non for profit research in agreement with EU and National laws and regulations concerning patients' data privacy and with the patients' informed consent given for the BD2Decide CLINICAL STUDY, also with the support of RECEIVING PARTNERS, upon agreement.

11. PROVIDING PARTNER and CLINICAL STUDY Coordinator shall maintain in their premises all CLINICAL DATA essential for the study for at least seven years after the end of the CLINICAL STUDY or for any such period as defined by the National laws of PROVIDING PARTNER. At the end of this period the RECEIVING PARTNER shall destroy the DATA.

Addresses of PROVIDING SCIENTISTs and RECEIVING SCIENTISTs are provided in Annex 1 to this Agreement.

10. General Terms

For what not expressly set out in this Agreement, the Grant Agreement and Consortium Agreement

terms and conditions will apply in relation to sharing and use of CONFIDENTIAL INFORMATION and DATA between the Parties.

In case the terms of this Agreement are in conflict with the terms of the Consortium Agreement, the terms of the latter shall prevail. In case the terms of the Consortium Agreement are in conflict with the terms of the Grant Agreement, the terms of the latter shall prevail.

Should any provision of this Agreement become invalid, illegal or unenforceable, it shall not affect the validity of the remaining provisions of this Agreement. In such a case, the Parties shall be entitled to negotiate a valid and practicable provision which fulfils the purpose of the original provision.

The provisions relating to Publication and Confidentiality, for the time period mentioned therein, as well as for Applicable law and Settlement of disputes shall survive the expiration or termination of this Agreement.

11. Enclosures

Annex 1 - List of providing Scientists and Receiving Scientists

Annex 2 - Implementing Letter

12. Signatures

IN WITNESS WHEREOF, the Parties have executed this Agreement, in one original for each Party, as of the EFFECTIVE DATE.

SCIENTISTS who will treat, provide, receive and share the DATA and CONFIDENTIAL INFORMATION, will sign for acknowledgement and acceptance this Agreement.

Annex 1 - List of providing Scientists and Receiving Scientists

1. List of Providing Scientists

PROVIDING SCIENTIST	Prof. Tito Poli
CLINICAL PARTNER	Azienda Ospedaliero Universitaria di Parma Via Gramsci 14 43100 Parma - Italy Tel. +39 0521 703109 e-mail: tito.poli@unipr.it

PROVIDING SCIENTIST	Dr. Lisa Licitra
CLINICAL PARTNER	Fondazione IRCCS Istituto Nazionale dei Tumori di Milano Via Venezian 1 20133 Milano (Italy) Tel. +39 02 23902150 e-mail: lisa.licitra@istitutotumori.mi.it

PROVIDING SCIENTIST	Prof. Ruud H. Brakenhoff
CLINICAL PARTNER	Stichting VU-VUMC Dept Otolaryngology/Head-Neck Surgery VU University Medical Center de Boelelaan 1117 1081 HV Amsterdam - The Netherlands Tel: +31-20-44 40953 e-mail: rh.brakenhoff@vumc.nl

PROVIDING SCIENTIST	Dr. Kathrin Scheckenbach
CLINICAL PARTNER	Heinrich.Heine Universitaet Duesseldorf HNO-Klinik Department of Otholarynhology - Head and neck Surgery Moorenstr. 5 40225 Düsseldorf - Germany Tel. +49 2118117570 e-mail: scheckenbach@med.uni-duesseldorf.de

PROVIDING SCIENTIST	Prof. Philippe Lambin
CLINICAL PARTNER	Stichting MAASTRO Radiation Oncology Dr. Tanslaan 12 6229 ET MAASTRICHT - The Netherlands Tel: +31 88 4455666 e-mail: philippe.lambin@maastro.nl

PROVIDING SCIENTIST	Prof. Marco Vitale
CLINICAL PARTNER	Università degli Studi di Parma Dipartimento S.Bi.Bi.T. - Via Gramsci 14 43100 PARMA - Italy Tel. +39 0521 033032 e-mail: marco.vitale@unipr.it

List of RECEIVING SCIENTISTS

RECEIVING SCIENTIST	Giuseppe Fico
TECH PARTNER	Universidad Politecnica de Madrid Departamento de Tecnología Fotónica ETSI Telecomunicación Avd. Complutense n30 28040 Madrid (España) Tel. (34)91 549 57 00 Ext. 3431 e-mail: gfico@lst.tfo.upm.es

RECEIVING SCIENTIST	Florian Jung
TECH PARTNER	Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e. V. Department Visual Healthcare Technologies Fraunhofer-Institute for Computer Graphics Research IGD Fraunhoferstr. 5, 64283 Darmstadt, Germany Tel. +49.6151.155.520 e-mail: florian.jung@igd.fraunhofer.de

RECEIVING SCIENTIST	Vassilis Tountopoulos
TECH PARTNER	Athens technology Center SA Rizariou 10, Chalandri 152 33, Athens - Greece Tel. +30 210 6874300 e-mail: v.tountopoulos@atc.gr

RECEIVING SCIENTIST	Avner Algom
TECH PARTNER	All-in-Image Ltd. Maskit 32 Hertzelia 46733 - Israel Tel. +972 50-428-2910 e-mail: avner.a@all-in-image.com

RECEIVING SCIENTIST	Luca Mainardi
TECH PARTNER	Politecnico di Milano Dip. di Elettronica, Informazione e bioingegneria Via Ponzio 34/5 20133 Milano - Italy Tel. +39 02 2399 3347 e-mail: luca.mainardi@polimi.it

RECEIVING SCIENTIST	Sergio Copelli
TECH PARTNER	Multimed engineers Srl Strada Cavallotti 11 43121 PARMA - Italy Tel. +39 335 294232 e-mail: s.copelli@multimedengineers.com

Annex 2 - IMPLEMENTING LETTER

This document must be attached to each transfer of DATA/CONFIDENTIAL INFORMATION.

RECEIVING SCIENTIST, name
full address to which data should be sent
Name of RECEIVING PARTNER
address
_____
_____
Tel.
e-mail_____

C.C. The Coordinator
Azienda Ospedaliero Universitaria di Parma (AOP)
Via Antonio Gramsci, 14, 43100 Parma (Italy)

Att.: _____

DESCRIPTION OF THE TRANSFER (To be completed by the parties)

Data subjects

DATA transferred concern the following categories of data subjects:

Head and neck cancer patients enrolled for BD2Decide study (retrospective and prospective cases) ad defined in the CLINICAL STUDY protocol approved by Ethics Committee.

Purposes of the transfer(s)

The transfer is made for the following purposes:

1. data analysis and prognostic models

2. estraction of population-related prognostic information and factors

3. identification of cancer phenotypes

4. identification and provision of radiomics prognostic features

5. extraction of gene prognostic signatures for head and neck cancer survival

Categories of DATA

DATA transferred concern the following categories of data:

- pseudonymized / encoded data comprising:
- clinical data, risk factors, imaging data and diagnostic images, pathology and histology data, treatment data (surgery, radio- and chemo-therapy), quality of life questionnaires, patients' follow-up data.

for MAASTRO only: radiomics raw data and radiomics signatures,

for INT only: genomics raw data, tumor registry data

for AOP only: population data in aggregated form derived from the following data sources:

- to be listed:

as described in the enclosed electronic CRF[4].

[4] the CRF is detailed in D2.1