Health by Advanced Therapies

D 1.1
Implementation of working groups addressing the main tasks of the Strategic Research & Innovation Agenda

Public

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1. Deliverable's description

The first Working Groups structure has been proposed during the Core Team meeting in February 2019 and further refined after discussions and suggestions by all contributing partners. The Working Groups structure as well as the leadership by Core Team Partners for each WG has been finalized at the end of April 2019.
A brief description of the WGs objectives (document enclosed to the current deliverable) has been prepared and shared within the RESTORE Supporters community.
We aimed to engage Supporters community to the Working Group activities, by collecting inputs and suggestions by the experts in the specific WGs fields, with the final objective to shape the RESTORE Roadmap Outline. To actively involve the supporters to the Working Groups activities we have collected the interest of supporters for specific Working Groups via a dedicated tool on the RESTORE portal, hosted on Supporters reserved area.

During the RESTORE Kick Off event (held on 6-7 May 2019 in Berlin) the present supporters could start the discussions that followed in the next months and involved all interested supporters and included in dedicated mailing lists.
It this way the RESTORE community participated in drafting the WGs outlines.

2. Working group outlines

The working groups outlines document is enclosed.

Health by Advanced Therapies

RESTORE
Working Groups Outline

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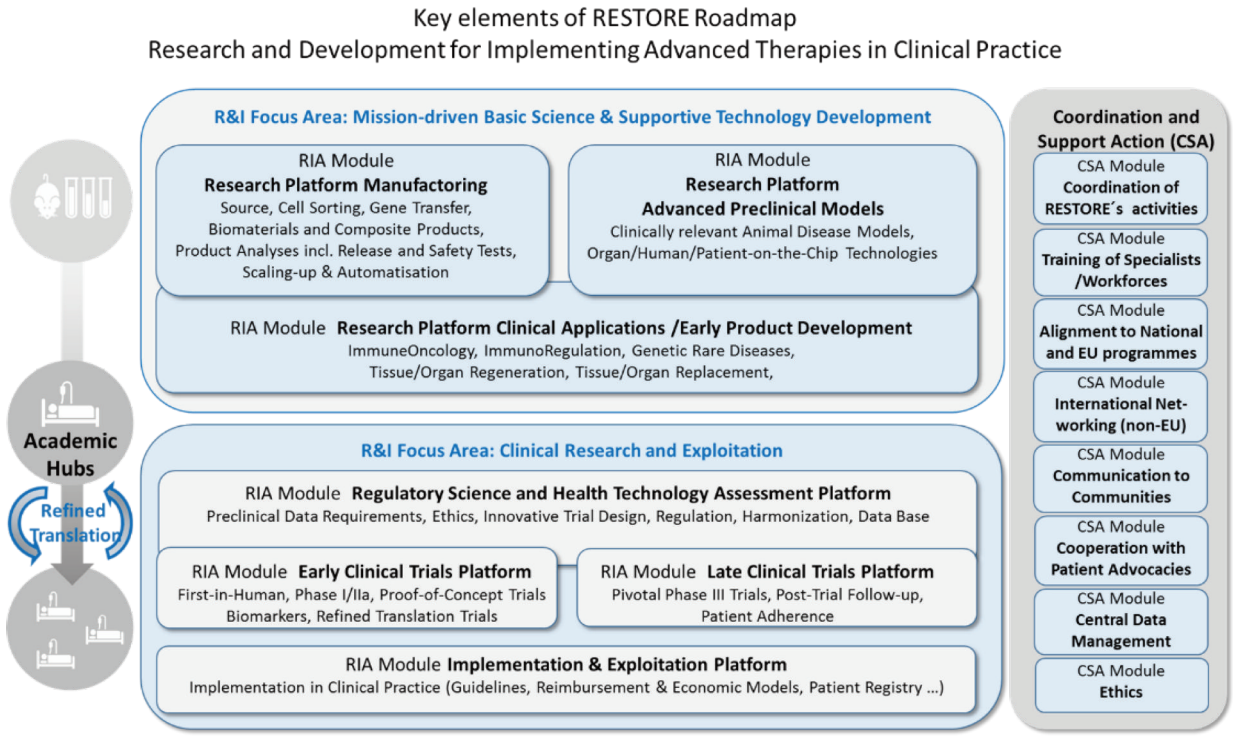
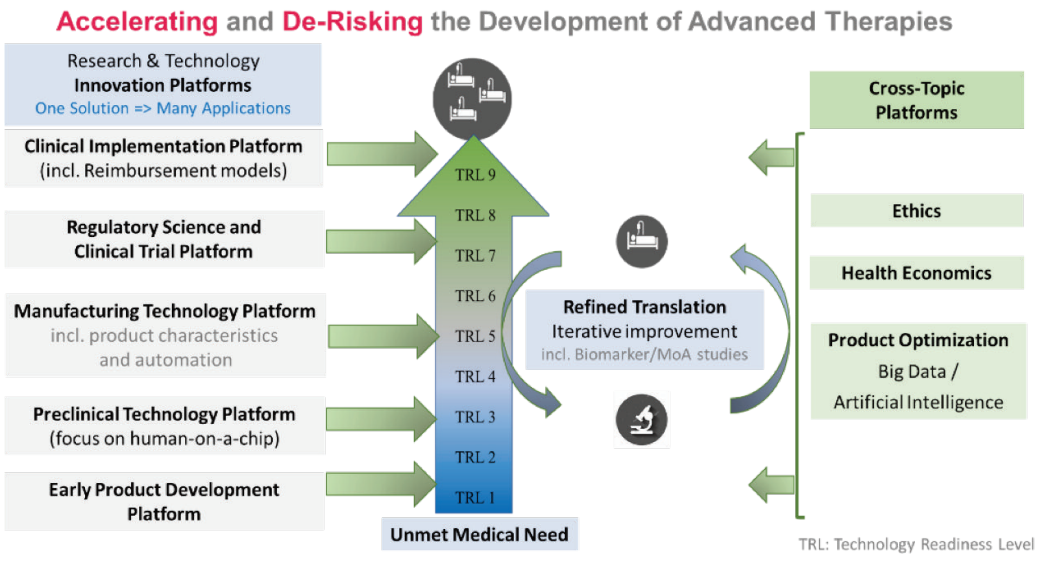
DESCRIPTION AND AIMS OF RESTORE WORKING GROUPS

The 12-month preparatory phase (start 1st March 2019) is structured to permit an inclusive, precise and transparent discussion and facilitate a quick start of the fully funded large-scale research initiative RESTORE in 2020/1. The working groups (WG) shall address the tasks of research and innovation actions proposed by RESTORE. The EC has accepted RESTORE's proposal to deliver the results of the work in a series of *strategy papers* as described below.



A key issue to achieve the vision and mission of RESTORE is the acceleration and de-risking of the development of new Advanced Therapies. RESTORE proposed three elements for this: i) Research and Innovation Technology Platforms (from Early Product Development platform to Implementation into Clinical Implementation Platform: one solution => many applications), ii) Refined Translation Tool (iterative improvement by a bench-to-bed-forward-to-bench approach in academic translational hub´s), iii) Cross-Topic Platforms (ethics, health technology assessment, big data/AI ...).



We aim for speedy drafting, with first versions being available over the summer of 2019. A first draft of an overview (without details) we need, according to the new information by the EC, already June 2019.

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1 RESEARCH AND INNOVATION TECHNOLOGY PLATFORM "MANUFACTURING" (WG 1-5)

All manufacturing WGs should address and discuss the following typical issues of manufacturing: Source of starting material, specific enrichment of targeted cells, gene manipulation, supportive materials e.g. biomaterials, product characteristics including product release tests and in-process controls, automation and scale-up of manufacturing, logistics of supply chain, strategies to test and lower immunogenic potential. An innovative aim is the smart manufacturing (AI project).

Each manufacturing WG should deliver a primary document (strategy paper) that addresses specific challenges related to the respective product class by i) outlining the immediate and plausible bottlenecks, ii) defining pathways for overcoming these bottlenecks, iii) propose exemplary but concrete draft calls for funding. For some WGs the delivery of additional, specific strategy papers is required.

1.1 WG 1: MANUFACTURING: SOMATIC AND GENE-MODIFIED CELLS

Lead: Pluristem, Co-Lead: Miltenyi, Inserm, Support: Catapult, Charité

- Cell source (immune cells, adult and IPSC derived)
- Quality and characterization of starting materials (i.e., Plasmids) and raw materials (i.e., key reagents)
- Definition of "master" cells applicable with few modifications for many indications (like Treg, CAR-T, stromal cells ...)
- Enrichment / sorting / cell culture conditions (e.g. cell expansion, preservation)
- Gene manipulation (gene transfer, gene editing ko/ki), vector/vector-free approaches
- Universal cell products (off-the-shelf, master cells with adapters e.g. CAR ...)
- In process control
- Product release criteria, potency tests
- Products stability (e.g. in-use stability data after thawing/reconstitution)
- In-depth characterisation (molecular and functional profiling, single cell analyses ...)
- Scale up / automation / scale out

1.2 WG 2: MANUFACTURING: TISSUE ENGINEERED & COMPOSITE PRODUCTS

Lead: Uni Zurich, Co-Lead: Uni Minho, Support: Charité

- Source of starting material (pluripotent/adult stem cells, master cell banks ...)
- Definition of "master" products applicable with few modifications for many indications (like heart valves, vessels ...)
- Universal cell products (pluripotent and somatic, off-the-shelf)
- Enrichment, selective differentiation
- Gene manipulation (gene transfer, gene editing ko/ki)
- Biomaterials/scaffolds
- Aimed structure (organoids, progenitor cells, differentiated tissue ...)
- In process control and product release tests
- Stability
- In-depth characterisation
- Scale up / automation / scale out
- Decrease immunogenicity/ inflammatory potency and increase engraftment

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1.3 WG 3: MANUFACTURING: *IN VIVO* GENE THERAPY

Lead: Telethon, Co-Lead: Charité, Support: Catapult, Miltenyi

- Definition of target cells
- Selection of vectors (AAV ...), vector development, non-viral delivery approaches (e.g. lipid nanoparticles ...)
- Gene editing *in vivo* (enhance/ enrich)
- Identification of potential non-viral delivery technologies and appropriateness for application to this field.
- Next-generation vectors with increased delivery efficiency, improved transgene bioavalability, higher tissue- and cell-type specificity, , switch on/off function, quantitative regulation ...
- Modification of the transgene to improve bioavailability upon gene delivery
- Route of administration *in vivo* (intraparenchymal, intrathecal, systemic; single vs. multiple administrations/ delivery routes)
- definition of "master" products applicable with few modifications for many indications (like AAV, for gene transfer, "safe harbor" approaches for gene editing ...)
- Safety: evaluation and minimization of acute and long-term toxicity, evaluation of effects on the target cells' biology
- Viral Vector Manufacture and Analytics - Assessment of anticipated requirements of product developers and gap analysis of current technologies to supply anticipated need
- Decrease Immunogenicity:: characterization and modulation of innate and adaptive immune responses to both delivery vehicles and transgenes
- Definition of "master" products applicable with few modifications for many indications
- Regulatory and ethical issues

1.4 WG 4: MANUFACTURING: PLURIPOTENT STEM CELLS

Lead: Inserm, Co-Lead: Telethon, Support: Miltenyi, Catapult

- European infrastructure of centers excellence (linked to GAIT) for clinical grade iPSC production from selected donors (screening, consent) - Master cell bank (qualification and release standard test) and working seeding bank for AMTPs
- Universal engineered IPSC (hypo-immunogenic, ...)
- Automated and closed human Pluripotent Stem Cell Manufacture (standardized scale-up analytical systems for the bioprocessing)
- Gene manipulation (genome editing Crisper Cas9, ...)
- Differentiation to targeted cells/tissues (harmonizing cost effective protocols, ..)
- Definition of "master" IPSC-derivative products applicable with few modifications for many indications (like heart muscle cells, Blood vessels, ...)
- Definition of derivatives products : intermediate progenitor cells, differentiated cells/tissue, organoids ...)
- Biomaterials/scaffolds => composite products
- Comparability of products derived from the MCB IPSC/ haplobank (potency assays, in-depth characteristics, in process control, product release tests)
- International Quality Parameters
- Data base of IPSC and derivatives for genetic and epigenetic stability
- Immunogenicity assays
- Standardized tumorigenicty testing
- Engraftment issues (biodistribution, *in vivo* cell fate, in vitro pre clinical models, ..)
- Regulatory purposes of IPSC and IPSC derived AMTPs (part of IND/IMPD filing) (link WG10)

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1.5 WG 5: MANUFACTURING: *EX VIVO* GENE DELIVERY/EDITING

Lead: Catapult, Co-Lead: Miltenyi, Support: Telethon, Catapult, Charité, Inserm

- Optimize cell culture conditions to maximize gene delivery/editing while reducing cell toxicity
- Next generation gene delivery and gene modification of cells for improved cellular properties and secretome by viral and non-viral vectors
- Gene editing technologies for KO/KI
- Improving gene modification/editing efficiencies
- Definition of "master" products applicable with few modifications for many indications (like CAR-constructs, mRNA transfer, CRISPR/Cas delivery ...)
- Identification of potential non-viral delivery technologies and appropriateness for application to this field.
- Viral Vector Manufacture and Analytics - Assessment of anticipated requirements of product developers and gap analysis of current technologies to supply anticipated need Characterize safety (e.g. genotoxicity for gene transfer/editing, suicide genes, off-targets/genomic stability for gene editing ...)

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2 RESEARCH AND INNOVATION TECHNOLOGY PLATFORM "PRECLINICAL MODELS" TO PROVE SAFETY, EFFICACY, MODE-OF-ACTION OF PRODUCTS FOR NEW ADVANCED THERAPIES (WG 6)

Successful and informative preclinical Toxicology and Proof-of-Concept studies are a prerequisite for the development of any new therapy, including new Adoptive Therapy approaches. However, conventional animal models are less useful for testing Advanced Therapies as they can only deliver data on homologues products (e.g. murine/NH primate iPSC-derived cell products, T cells etc.) with limited predictive value for safety and efficacy. Although the use of "humanised" mouse models improved the model systems, they still suffer from limitations because of the partly xenogeneic situation (with impact on homing, intercellular crosstalk etc.) and unfaithful disease models. *In vitro* model systems are based mostly on traditional 2D-cultures, which do not adequately simulate the *in vivo* situation. Generating physiologically relevant disease models is a promising approach to improving our ability to detect and predict drug induced toxicity and efficacy and the mechanisms behind. Therefore, there is a high need for improved preclinical models, particularly complex *in vitro* physiologic and disease models.

2.1 WG 6: PRECLINICAL MODEL SYSTEMS: *IN VITRO* AND *IN VIVO*

Lead: TissUse, Co-Lead: Inserm, Support: Telethon, Catapult, Miltenyi, Charité

Completion of selection and description of regulatory acceptable "contexts of use" for advanced animal vs human/patient-on-a-chip model developments with fit to preclinical developments and pivotal clinical trials.

- Clinically relevant animal disease models (large animal models, humanized murine models, immunoaged mouse models)
- Clinically relevant *in vitro* models based on organoids Organ/Human/Patient-on-Chip Technologies
- Identification of relevant patient specific -IPSC and tissue derived normal and cancer organoids for clinical application (link WP 7-9)
- Suitable for Advanced therapy product screening and candidate selection
- Suitability for drug screening (combo-therapy) and toxicology (link WP 4)
- Suitability for regulatory purposes (part of IND/IMPD filing)
- Relation of preclinical data to product characteristics (AI project)

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3 RESEARCH AND INNOVATION TECHNOLOGY PLATFORM "CLINICAL APPLICATIONS/EARLY PRODUCT DEVELOPMENT" (WG 7-9)

Uncovering the molecular basis of diseases and revealing new opportunities to restore health. Special focus is given to targeted gene therapies in rare diseases, endogenous regeneration, replacement strategies, and cancer. The generation of "master" products suitable for many applications by minor adaptation are one focus.

3.1 WG 7: ENDOGENOUS REGENERATION

Lead: Charité, Co-Lead: Pluristem, Support: Telethon, Charité

- Direct support of endogenous regeneration by targeted tissue growth factors
- Targeted elimination of diseased/pathologic cells to favor endogenous regeneration
- Strategies to protect endogenous cells from immunorecognition/toxic agents
- Indirect support of endogenous regeneration by pro-vascular or immunotherapeutic approaches
- Definition of "master cell and derived" products applicable by minor manipulation for different indications (like MSC, PLX, Treg, EV-derived cells ....)
- Supportive "paracrine factors" for improved *in vivo* functionality (growth factor release, better survival...)
- Defining functional Potency test
- Composite product approaches (e.g. biomaterials + cells, or extra-vesicules, exosomes..)
- Selection of medical indications (criteria for)

3.2 WG 8 GENE/CELL/TISSUE REPLACEMENT STRATEGIES

Lead: Telethon, Co-Lead: Uni Zurich, Support: Miltenyi, Inserm

- Definition/further characterization of diseases' pathogenic mechanisms using relevant *in vitro* and *in vivo* models
- Source of stem/ progenitor cells for targeted gene "repair" in patients with rare diseases and chronic diseases including cancer (e.g. immune rejuvenation..).
- Definition of "master cell" products applicable with minor manipulation to different indications (like HSC, iPSC, ESC, adult liver SC, adult skin/ limbal SC ...)
- Strategies to promote *in vivo* engraftment/expansion of engineered cells/tissues
- Strategies to decrease immunogenicity of cells/tissues
- Improve cell/tissue engineering strategies (develop stealth gene transfer/editing procedures, further optimize culture conditions to preserve cell fitness/genomic integrity and increase gene transfer/editing)
- Source of cells and scaffold for tissue replacement strategies (tissue engineering)
- Definition of "master" engineered tissue product applicable with minor modifications to different indications (e.g. vessels ...)
- Composite product approaches (e.g. biomaterials + cells)
- Combinations of *ex vivo* and *in vivo* tissue engineering (promote terminal differentiation/organization of *ex vivo* assembled structures *in vivo*)
- Development of host conditioning procedures to enhance cell/tissue engraftment
- Definition of mechanisms leading to immune-rejection/short-term stability of transplanted cells/tissues

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- Selection of medical indications with focus on inherited diseases, autoimmune diseases, viral infection diseases, metabolic diseases, neurodegenerative diseases, aging
- *In vivo* advanced gene replacement, genome/mRNA editing approaches (e.g: nucle-ase-free, base correctors...)
- Non-invasive biomarkers to monitor advanced therapy efficacy
- Challenging gene therapy: compromised target organs (e.g.: advanced fibrosis), large gene,
- Molecular bases of known or new genetic diseases (*in vivo* and *in vitro* models)

3.3 WG 9 CANCER

Lead: Miltenyi, Co-Lead: Inserm

- Definition of "master cell" products applicable by minor manipulation for different indications (universal cells: e.g. non-immunogenic allogeneic off-the-shelf CAR-T or TCR-T, adapter-CAR-T, IPSC derived immune cells (DC NK, T for CAR ...)
- Strategies to avoid bystander effects on normal cell/Tissues
- Strategies to harness immune system for cancer therapy (Cancer Vaccine, combo-therapy, adoptive and non-adoptive therapy)
- Selection of optimal starting cell population cell subtypes (e.g. memory stem T cells ..)
- Supportive factors for improved *in vivo* functionality (growth factor release, better survival...)
- Identification of new targets on tumor cells, hematologic malignancies, and TME.
- Treatment strategies for solid tumors
- Tissue regeneration post-tumor cell killing
- Selection of tumor entities (criteria for)
- Patient stratification/tumor characterization (NGS, immune phenotyping ...)
- Immunocompetent animal models and complex organoids for immune therapy strategies (link WP6)

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4 RESEARCH AND INNOVATION TECHNOLOGY PLATFORM "REGULATORY SCIENCE AND CLINICAL TRIALS"

Defining the needs and strategy of clinical research for the development of Advanced Therapies, the package encompasses four fields - regulatory science, health technology assessment, early/late clinical trials, and marketing authorization. An important de-risking tool is the Refined Translation approach (iterative improvement of product/patient selection/protocol based on the feedback information by mechanistic side studies (biomarkers) during early clinical development before moving to risky and expensive late clinical trials).

4.1 WG 10: CLINICAL RESEARCH: REGULATORY SCIENCE AND EARLY HEALTH TECHNOLOGY ASSESSMENT (HTA) & EARLY CLINICAL TRIALS AND REFINED TRANSLATION

Lead: Charité, Co-Lead: Catapult, Support: Telethon, Catapult, Pluristem, Miltenyi

Subtask Early Clinical Trials and Refined Translation (Charité)

- Mechanistic side studies including therapy monitoring by biomarkers
- Link of clinical and biomarker results to preclinical data and product characteristics (microheterogeneity) (AI project)
- Criteria for Academic Translational Center of Excellence (EU criteria of Center of Excellence
- Standards for preclinical requirements for adult and IPSC / Derivatives (link to WG6, WG4)

Subtask Regulatory Science and early HTA (Catapult and Charité)

- Criteria for early HTA (target indication, medical need, cost of goods)
- Improvement and homogenization of regulatory rules in Europe - what would be wish, what might be realistic?
- Innovative early clinical trial design and biometry (i.e., use of validated surrogate endpoint, small population, etc)
- Harmonise GMO requirement across EU during clinical development (i.e., Directive 2009/41 on contained use of GM-microorganisms and Directive 2001/18/EC on deliberate release of GM-organisms)
- Map the overlapping areas between regulatory provisions for ATMP drugs (i.e., Dir 2001/83/EC, Regulation (EC) No 1394/2007, Regulation (EC) No 726/2004, etc), Transplant (i.e., Dir 2004/23/EC) and GMO (i.e., Directive 2009/41 on contained use of GM-microorganisms and Directive 2001/18/EC on deliberate release of GM-organisms)

4.2 WG 11: CLINICAL RESEARCH: PIVOTAL CLINICAL TRIALS AND MARKETING AUTHORISATION

Lead: Telethon, Co-Lead: Pluristem, Support: Miltenyi, Charité, Catapult

- Facilitators for pivotal trials (Adaptive Pathways, Prime etc.)
- Innovative pivotal trial design (statistics etc.)
- Patient stratification markers for selection of appropriate patients by prediction safety/efficacy issues
- Product supply process (scaling-out)
- Validation of surrogate endpoints (for ATMP under development for rare/ultra-rare diseases) by EMA
- Use of validated patient / disease registries for registration purposes (i.e., validation of EBMT registry modifications for CAR-Ts) - linked to WG 12

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5 RESEARCH AND INNOVATION PLATFORM "IMPLEMENTATION AND EXPLOITATION OF ADVANCED THERAPIES"

Reimbursement, successful implementation into clinical routine and long-term follow-up on patients

5.1 WG 12: POST-TRIAL AND LONG-TERM FOLLOW-UP, DATA WAREHOUSE AND PATIENT REGISTRY

Lead: Telethon, Co-Lead: Pluristem, Support: Catapult, Miltenyi

- Review of existing regulatory standards and their suitability to Advanced Therapies
- Common clinical study warehouse (not just trial registry, but results from mechanistic side study data, clinical outcome)
- Long-term safety and efficacy data by the use of validated patient/disease registries for treatment outcome readout and patient adherence hereto.

5.2 WG 13: IMPLEMENTATION OF NEW ADVANCED THERAPIES INTO CLINICAL ROUTINE

Lead: Miltenyi, Co-Lead: Telethon, Support: Catapult, Pluristem

- Inclusion of new therapies in therapy guidelines
- Synergies with implementation of precision medicine in clinical practice
- Scale-up and scale-out of qualified ATMP manufacturing all over Europe
- Conditions for hospital exemption and conditional approvals to initially foster patients´ access to novel curative therapies
- Highly specialized Centers-of-excellence for controlled delivery of novel Advanced Therapies
- ATMP treatment centres may be available in only one or some regions, due to low prevalence and/or need for specialised centers, hence the need to move the patients to the highly specialised clinical centers through the currently available EU patients mobility provisions (i.e., Directive 2011/24/EU "cross-border" or Regulation on the coordination of social security systems)

5.3 WG 14: VALUATION AND INNOVATIVE REIMBURSEMENT MODELS FOR NEW ADVANCED THERAPIES

Lead: Charité, Co-Lead: Catapult, Support: Telethon, Pluristem, Miltenyi

- Value added determination and benchmarking of Advanced Therapies
- Innovative reimbursement models for ATMPs
- National/EU funds to overcome regionalization and to avoid that the Regional Health Funds of the ATMP treatment center or the Treatment center itself bears the cost for patients from all regions

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6 CROSS-TOPIC PLATFORMS: ETHICS, HTA, BIG DATA/AI

6.1 WG 15: ETHICS

Lead: External expert

Ethical issues concern almost every aspect of Advanced Therapies, from the use of human material in preclinical research, through ethical considerations in the design of clinical trials, to reimbursement, accessibility and marketing of authorized products. In addition to known, albeit hard-to-answer, ethical question, there exist further, less-known questions that may arise from practical constrains in the development Advanced Therapies. Moreover, as the field advances, new questions and issues which are currently still unknown or not yet relevant, will arise. That makes ethics in Advanced Therapies a live and evolving field of research. In addition, with the research and healthcare shifting towards patient centricity, open dialogues and discussions with patient communities for the uptake of Advanced Therapies. Early involvement of patients as a stakeholder in the development encourages transparency and further de-risking in the roadmaps to be developed by each WGs.

6.2 WG 16: BIG DATA/AI

Lead: Pluristem, Co-Lead:Catapult, Support: Charité, TissUse, Miltenyi, Telethon, InnActa

The Advanced AI work package aims to enhance the development of clinical applications of "new living drugs" by providing advanced tools to select the optimal living drug for a targeted chronic disease and the most suitable patient population that can be cured by advanced living drugs therapy. We will apply Advanced AI to complex datasets while ensuring security and privacy of personal data.

Cutting edge computational models will be used to derive prediction models integrated with Big Data, Artificial Intelligence (AI) and Machine Learning (ML) to characterize the disease trajectories and cure pathways of a large patient population over an extended period of time.

State-of-the-art, point of care data collection technologies will be integrated by using the Internet of Things (IOT) to enable "on-line" follow-up and monitoring of patients cure progress during clinical studies and for Large scale implementation and cost-effective advance therapies.

Due to the sensitivity of such data, proper procedures secured by Internet Protocols (IP sec) will be in place to ensure that all ethical concerns are addressed appropriately. This ensures that the project complies with relevant national and EU guidelines and legislation (e.g. GDPR).

The project will establish an Ethics Board headed by a Data Protection Officer (DPO).

The DPO will guide the RESTORE consortium on how ethics-related matters should be handled. In addition, an external independent ethics advisor will be assigned to the consortium.

The overall aim of this work package is to enable the modeling and prediction of responders to the advance treatment

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