TECHNICAL ANNEX

1. S&T EXCELLENCE

1.1. Challenge

1.1.1. Description of the Challenge (Main Aim)

Over the past decade within the developing scenario of regenerative medicine, perinatal (Pn) tissues have been shown to harbour a vast array of cells with therapeutic potential. Even though historical clinical evidence, preclinical studies, and a few ongoing clinical trials support this potential, there are still many open questions. The time has now come to combine the expertise and efforts to create a solid, multidisciplinary network that will act as a coalition for individual teams.
The INTERNATIONAL PLATFORM FOR TRANSLATIONAL MEDICINE OF PERINATAL DERIVATIVES (NATAL), which includes participants with extensive know-how in basic research, clinical trials, veterinary medicine, regulatory affairs, and the biomedical industry, will join forces to strengthen the knowledge in the field, and overcome the bottlenecks of translation to provide innovative therapeutic applications of Pn-derived tissues, cells, and factors.
Pn tissues are a large and diverse family, and this Action will focus on the following ***Pn Derivatives (PnD) from term pregnancies:*** *amniotic membrane, chorion, Wharton's jelly, amniotic fluid, and the cells isolated from these tissues, and the factors that these cells release.* PnD offer several advantages, such as their easy and non-invasive procurement, abundance, and favourable ethical status. Furthermore, PnD have drawn much attention due to their reduced immunogenicity and immune-modulatory properties, making them attractive candidates for allogeneic transplantation.
European research on PnD has delivered a precious reservoir of knowledge and expertise, and considering that most players are in this Action, the challenge is now to streamline the transition from bench to bedside, and to provide insight the mechanisms underlying their therapeutic potential.
The main aim of NATAL is to implement an integrated scientific, medical, and industrial global network to comprehensively investigate and exploit the therapeutic potential of PnD.

1.1.2. Relevance and timeliness

Research on the therapeutic applications of PnD is gaining momentum, as documented by the increase in publications and the number of completed or ongoing clinical trials. Indeed, the multidisciplinary knowledge gained in the past years by the main actors of the scientific, clinical, and industrial research on PnD will constitute a powerful network. This network has an interdisciplinary plan of action which will address open questions (e.g. consensual terms for classification, comparison, standardised operative procedures for harvesting, processing, cryopreservation), monitor and build upon ongoing studies (e.g. from comparison of preclinical studies and identification of mechanisms of action, up to the translation into European clinical practice by addressing regulatory issues and stakeholders' view), and thus ultimately promote more efficient, safer, and faster advancement of their therapeutic applications, and attract industrial investments.

1.2. Objectives

1.2.1 Research Coordination Objectives

The NATAL collaborative framework aims to facilitate interactions among the different groups working on in vitro characterization, preclinical studies, veterinary medicine, clinical development, and regulatory and ethical issues. Specific research objectives are:
1. To define standards for the processing and in vitro characterization of PnD;
2. To collect and analyse preclinical data from different groups in order to provide a clear understanding of the therapeutic potential and underlying mechanisms in different models;
3. **To collect data from completed trials** in order to provide an understanding of which PnD could offer the optimal therapeutic effects in **veterinary medicine**;

4. To foster networking between those who perform clinical trials in order to review, discuss and develop new and/or improved clinical strategies based either on Pn cell differentiation (e.g tissue engineering approaches) or on their paracrine-acting features (e.g. use of cells/factors for regenerative medicine approaches);
5. To synergize regulatory experts, selected Patients' Associations, researchers, GMP material providers, and clinicians in order to guide the latter for the successful implementation of efficient and safe clinical trials.
Overall, **this Action will acquire knowledge from basic and applied research that will be the foundation of the development of clinical applications with ultimate benefit for patients.**

1.2.1. Capacity-building Objectives

NATAL consists of multidisciplinary experts linked by their mutual interest in PnD, that work jointly to deliver a PnD enabling research environment. Capacity is built on existing assets, such as human resources, institutional funds, facilities, and infrastructures, and the presence of participants in other research networks and scientific societies.
Specific capacity-building objectives are:

- To improve personnel skills and competence, in particular for young researchers;
- To enhance researcher access to knowledge and information;
- To facilitate access to established worldwide research infrastructure networks;
- To promote access to tissues, cells, bioactive factors, animal models and materials;
- To create opportunities for a constructive dialog among scientific and medical communities;
- To bridge the gaps between research and translation into clinic;
- To foster the uptake of research results, especially by industry and SMEs;
- To communicate and disseminate research findings.

Overall, NATAL will create a "PnD-favourable network" to promote sustainable research development by enhancing the abilities of individuals and organizations to efficiently and successfully undertake and disseminate high quality research.

1.3. Progress beyond the state-of-the-art and Innovation Potential

1.3.1. Description of the state-of-the-art

Over the past century, amniotic membrane patches from human placenta have been used as a biomaterial in clinical practice to heal skin wounds, burn injuries, and chronic leg ulcers [1, 2]. Since then, other PnD have been widely investigated, for reasons including their differentiation capabilities and paracrine effects, the latter of which have been shown to be attributed to their immune-modulatory, anti-apoptotic, and angiogenic properties. Immunomodulation by PnD has paved the way for many pre-clinical studies on their therapeutic potential in inflammatory-based disease models, e.g. autoimmune[3], neurological[4-7], hepatic[8-10], pulmonary[11-15] , cardiac[16, 17], degenerative joint[18, 19], intestinal[3, 20], and muscular diseases[21]. There are currently 40 recruiting and ongoing clinical trials registered on https://clinicaltrials.gov/, using selected or mixed PnD populations, predominantly in diseases based on immune-alteration but also in disparate etiologies. The results available thus far are promising in regards to overall PnD safety and therapeutic potential and are pressing for growing applications. However, further studies are necessary to understand the underlying mechanisms (cell differentiation or paracrine actions), of the observed PnD therapeutic effect in order to fully exploit their therapeutic potential with opportune procedures (e.g. tissue engineering, secretome delivery). The current need is to create a forum for the free exchange of expertise and collate the research outputs from large-scale studies for comparing PnD in different therapeutic approaches in vitro and in vivo, setting GMP and QA/QC standards, as well as initiating multi-center clinical trials for selected conditions using a specifically identified PnD.

1.3.2. Progress beyond the state-of-the-art

The numerous international participants and the involvement of stakeholders will warrant the development of standardized paradigms leading to more effective efforts, as a result of research defragmentation. This, together with the multidisciplinary nature of the consortium, and the combination of its areas of expertise, can progress in the following domains:
Knowledge of PnD. The availability of standardized protocols for processing and in vitro characterization is expected to better define the traits and features of different PnD, by allowing comparison of independent studies and pooling data.
Identification of the PnD therapeutic potential for a specific pathological condition. Coordinated reference centres will screen PnD in order to compare and integrate results obtained by different in vivo studies.
NATAL will focus on two PnD applications: (i) tissue engineering approaches exploiting their differentiation capabilities into tissue-specific cells, and (ii) paracrine actions of PnD cells whereby they release mediators acting on resident and/or progenitor cells. The Action will identify the optimal strategy and PnD for the currently tackled diseases, and opening new possibilities for PnD applications to other diseases.
PnD-based therapies in veterinary practice. The expansion of veterinary medicine applications is expected to come through pooled preliminary data showing benefit in case studies. This information will also provide knowledge on the application of PnD in clinical settings.
PnD-related health economy. The Action will streamline translation of pre-clinically validated therapeutic approaches. Clinicians will act as catalysers and promote the organisation of multi-center trials, while SMEs will enthral other companies with marketable solutions. The involvement of patient associations could steer the public opinion for the implementation of PnD-based therapies. Addressing regulatory issues and positioning them into the “EU Standard for Clinical Research with PnD” will provide regulations for PnD-related exceptions and assure compliance of the products and protocols under development. This system will focus on tissue engineering applications (i.e. Pn cell differentiation for regeneration of damaged tissues) and paracrine actions of PnD secretome.
Awareness about PnD use. The public sensitization campaign, ethical debate, patient’s and stakeholder’s views will put attention toward PnD, increasing bio-banking and demand.

1.3.3. Innovation in tackling the challenge

Networking the main actors of the articulated process from bench to bedside has proven successful for the development and application of most therapies. Innovation in NATAL relies in:
The Action experimental strategy, which overall consists in coordinating and standardizing the research processes from cell biology to clinical application. It will specifically (1) trigger the exchange of expertise and methods to compare pre-clinical features among PnD cell populations; (2) provide a research-based decision system regarding the use of either one or combined PnD for developing therapeutic approaches for specific animal or human diseases; (3) collect relevant clinical data from large-scale and long-term trials with PnD. Tangible outputs will be issued from coordinated, multidisciplinary approaches and multi-center collaborative studies, using traditional and forefront techniques made available by the partners.
The innovative expected outputs. Each Working Group will strive for the development of ground-breaking knowledge and advanced products e.g. cell-free treatments, new medical devices involving biomaterials, including nanotechnology, and commercial kits for PnD characterization. The knowledge management and exploitation task force, and the industrial investments of the participating SMEs should initiate commercial pipelines of PnD-based and –related products.
The pushing force of stakeholders’ interest. In this framework, scientific and technological innovation is sustained by regulatory expertise, lab/clinical training, ethical approval, economic investments and end-users’ awareness and acceptance.

1.4. Added value of networking

1.4.1. In relation to the challenge

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A PnD-focused network this large has yet to be established. All participating groups have excellent research capacities, including highly trained personnel, state-of-the-art equipment, and an extensive know-how on PnD. Therefore, **a tight-knit network of multidisciplinary, international collaborators will provide valuable insights into PnD biology and therapeutic mechanisms. This will ultimately lay the grounds for safer, and possibly broader, clinical applications of PnD.** Two main therapeutic approaches, Pn cell-based tissue engineering approaches and PnD paracrine actions, are currently being studied by the consortia for different pathologies, so this Action will not be limited to a specific pathology, but rather initially to the identification of the most suitable strategy and PnD for the currently studied diseases, and then to widening PnD applications to other conditions.

1.4.2. In relation to existing efforts at European and/or international level

PnD is a topic of interest in several well-established, international scientific societies, including those with a broad focus (e.g. ISSCR, ISCT, TERMIS), those focusing on cell and tissue banking (e.g. EATB), to those more specifically focused on placental stem cells (i.e. International Placenta Stem Cell Society (IPLASS) and International Perinatal Stem Cell Society (IPSCS)). However, while the former ones do not specifically direct their efforts towards PnD research and translation into clinical and industrial practice, the latter are mainly devoted to the dissemination of scientific achievements within the scientific community which only fosters the spontaneous and sporadic collaboration between scientists on a more individual (group-to-group) basis.
NATAL would be the first collaborative network in Europe and worldwide to become a structured “aggregating nucleus” which aims to actively and continuatively link different European research groups working in the PnD field, thus enabling information flow, troubleshooting, and standardisation of protocols, and fostering the translation into clinical and industrial practice.

2.1. Expected Impact

2.1.1. Short-term and long-term scientific, technological, and/or socioeconomic impacts

Each WG has short term impacts (Action lifetime, up to 2 years after) and concur to the long-term outcomes (3-6 years after the Action). Impacts will endure and amplify as the Action becomes a hallmark of worldwide PnD research.
Scientific impacts. Short term: - Effective integration and dissemination of European research, by combining existing information on PnD characterization (WG1), pre-clinical evaluation (WG2), veterinary medicine (WG3), and clinical trials (WG4), and making it available through virtual tools (e.g. atlas, virtual facility), and publications. - Creation of highly qualified reference labs for characterization of specific traits of PnD (e.g. immunological properties, differentiation). - Spreading of excellence by the establishment of active and efficient knowledge exchange through workshops, conferences, seminars (all WGs). - Filling research and knowledge gaps by implementing goal-oriented actions and merging knowledge and competences (WG1 to WG5). - Common reference platform for regulatory matters (WG5) for clinical study design.
Long Term: - Defining mechanisms (e.g. differentiation or paracrine) underlying the therapeutic effects observed in vivo. This will provide rationale and research-based platform regarding the several potential uses of PnD.- Increase scientific symposia on PnD at society meetings focused on cell therapy, tissue engineering and regenerative medicine.
Clinical impacts. Short term: - Improved understanding of the relationship between different PnD and therapeutic application(s) (WG1, WG2, WG3, WG4). - Establishment of experimental (WG4) and regulatory and ethical (WG5) conditions for multi-center clinical trial(s) for Pn cell transplantation and regenerative medicine. - Reinforcing veterinary capacity for multi-center trials in companion and large animals (WG3).
Long Term: - Assessment of efficacy and release of established protocols.
Technological impacts. Short term: -Contribution to standards and harmonization of methodologies under GLP (Good Laboratory Practices) for cell isolation, in vitro culture, and characterization for reproducibility and comparison of data (WG1, WG5). - Availability of GMP

conditions (e.g. tissue collection, transport processing, cell isolation and culture, derivative collection) for clinical-grade products (WG1, WG5).
Long Term: - Development of new cell media preparations and supplements and bioreactor/ex-vivo perfusion technologies in order to obtain functional cellular products which maintain the cells in physiological conditions. - Development of biotechnologies for cell-free approaches to obtain paracrine regenerative factor(s) and microvesicles/exosomes as advanced medicinal products.
Economic impacts. Short term: - Establishment of PnD bio-banks for research and clinical purposes (WG1, WG5). - Producing patents and spin-offs to bridge the gap between basic research, clinic, and biomedical industries (WG1, WG2, WG4, WG5) - Creation of jobs in the private and public health-care sector.
Long Term: - Inclusion of cellular and cell-free PnD-related products into the portfolio of bio-tech companies. - Acceleration of the European economic growth in regenerative medicine, including that of small and medium sized enterprises, through product innovation and market investments.
Social and Ethical impacts. Short term: - Tackling of ethical issues, promoting codes of conduct and best practices for the scientific community, provision of information (e.g. publications, web posts) for legislation and contribution to ethical debates in the society at large (all WGs). - Training and educating students of European and non-European countries through the organization of Summer/Winter schools and educational tools and activities, raising the awareness in ethics (all WGs). – General public active involvement with PnD donations.
Long Term: - Patient Associations recognition and endorsement of PnD as treatments for specific diseases that will show to benefit from the PnD-based strategies (WG5 and WG6). - Refinement, Reduction, and Replacement (3R) of animal use in research on PnD as networking to compare and discuss results and working together to answer open questions will allow for less redundancy in experiments with animals (WG2). The identification of reference research labs in WG1 will allow for in vivo studies to be performed with fully validated PnD, thus allowing for comparison of results with other groups who are performing in vivo studies with the same validated batches.

2.2. Measures to Maximise Impact

2.2.1. Plan for involving the most relevant stakeholders

The Action impacts will be maximized through dissemination, communication and exploitation. The identified **stakeholders** are scientists, clinicians, veterinarians, students, industries, lay-men, and patients:
a) The scientific community beyond the Action's participants will thrive from acquired knowledge on PnD and insights into the mechanisms of action. This will be obtained through scientific papers (D1d, D2c), consensus procedures and research priorities (D1b, D2b), the "In Vitro" (D1a), "In Vivo" (D2a) sections of the a public website (D6b), virtual tools (D1c), conferences (M6g, M6h), and will involve the interaction of the Action with other PnD-related international initiatives (Task 6.1). The latter will be assured by the fact that most of the NATAL participants have positions in international societies and European consortia focused on reproductive medicine, PnD research, mesenchymal stem cells, banking, cell-based therapy and technology, and immunology.
b) Clinicians will profit from pre-clinical and clinical data, which will be disseminated by peer-reviewed publications (D1d, D2b, D2c) and scientific meetings (M6g, M6h). Advanced cell therapy practices will be facilitated by the "Clinical" part (D4a) of the network register (D6d), and the establishment of standard operating procedures (Quality Control (QC) and Quality Assurance (QA)) for cell cultures (D5a) and EU standards for clinical research (D5b).
c) Veterinarians will exploit data from preclinical studies in laboratory animals into veterinary advanced practice, and will publish reports on advanced therapies with PnD in small, medium, and large animals (i.e. race horses, cats, dogs, cows). They will contribute to the same activities as basic scientists and clinicians, in addition to publications (D3b) and the "Veterinary Medicine" part of the network register for veterinary clinic (D3a).

d) Students and young researchers will receive training in cutting-edge PnD research and translation. They will have dedicated educational tools (D6.f) and the possibility to participate in "a day in the lab" events (M6c, M6d) as well as educational courses (D6a, D6b).
e) Biomedical industries are stakeholders that could exploit the harmonized standards and procedures to develop new products quicker. The NATAL SMEs encompass tissue banking, cell therapy-related products for in vitro research and clinical use and tissue processing equipment. They are expect to act as "industrial pioneers" and their representatives, identified at the Kick Off Meeting, will be involved in the network early on (T6.3) through the dedicated "Science and Industry" workshop (M6f) and a specific "Business opportunities" showcase on the website for possible research-industry partnership aimed to student training, industry-financed research, IP exploitation, joint products development as e.g. kit reagents, banking cells (D6e).
f) The society at large, including patients, and donors/mothers-to-be of Pn tissues will be informed on the debate regarding ethical aspects on the use of PnD and on research progress for the development of cell-based therapies (T5.4, and the informative day M6e). They will be provided with dedicated flyers (D6c) containing unbiased, non-commercial scientific information.
g) Patients will benefit from innovative, cell-based regenerative and immunomodulatory therapies for diseases which are not yet adequately covered by conventional protocols. Patient associations will join the Action during the second year, once the clinicians have identified which disease(s) could be best treated with selected PnD. European patient perspectives are subject of T5.5 and will be disseminated in T6.4 to other patients and all other described stakeholders.

2.2.2. Dissemination and/or Exploitation Plan

Each beneficiary will be called to contribute directly to the exploitation/dissemination activities. The IPR (Intellectual Property Right) Team will manage the processes relevant to IP exploitation and translation; WG6 Leader will coordinate the dissemination of the scientific knowledge.
Yearly dissemination and exploitation plans will be prepared (WG6) with the purposes of: 1) boosting basic and industrial research on PnD by sharing knowledge with scientific and medical research communities; 2) promoting private investments, levering on the innovative outputs of the Action and the appealing advanced therapies market; 3) increasing PnD awareness and acceptance, focusing on clinical efficacy and safety. The plan will contain the following:
SECTION I – DISSEMINATING THE FOREGROUND: innovations beyond the state-of-the-art, target groups, detailed agenda (e.g. which congresses to attend; when to organise the summer school), tools (e.g. online atlas, peer-reviewed publications), channels (e.g. attendance to scientific events, use of contact reference persons), actions (e.g. organisation of a symposium, participation in ethical debate), and actors (which Participant does what).
SECTION II – PATHWAY TO EXPLOITATION: exploitable results, IP owner(s) plan for exploitation (eg. IP protection, commercial arrangements), exploitation detailed agenda, actions and actors.
SECTION III – EXPECTED IMPACTS: analysis of results impacts per stakeholder group, contribution to standards, risk-analysis and contingency plans.
SECTION IV: DISSEMINATION & EXPLOITATION BY EACH BENEFICIARY: individual plans.

2.3. Potential for Innovation versus Risk Level

2.3.1. Potential for scientific, technological and/or socioeconomic innovation breakthroughs

General risk and payoff. To be successful, NATAL must bridge the gap between research and clinic with the very ambitious actions described above. Therefore, innovation in NATAL is overall a risk-taking process. However, it is ground for breakthrough PnD-based therapies to treat life-threatening conditions and enhance the quality of life for many people. **Intrinsic risks** are:
High investment for networking in a field with shortage of funds for experimental research. NATAL teams are established groups that have attained concrete scientific evidence with their own resources. Each WG is implemented by many of those teams that will keep striving for research funds thus assuring the delivery of the planned networking outputs. Thus, **strong scientific input is guaranteed and will clearly bring ground-breaking knowledge and advanced products**.

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Not yet identified clinical applications for the Action. Several different PnD are in the process of being experimented in a variety of unrelated clinical trials. The Action aims to experiment a collaborative research-based system to identify the best therapeutic approach for a specific condition based on PnD potential to differentiate into tissue-specific cells or to induce bystander effects through their paracrine action. Simultaneously, the action will lower the barriers for manufacturer, clinicians, regulators and patients for the implementation of new approaches for some identified pathologies in the context of health systems. These determinants of new health, ethical, and cultural frameworks **are innovation breakthroughs with a trade off to the society as an added value to the novel cell based therapy**.
Limited market uptake of the developed technology innovation. NATAL has a strong focus on business science collaborations, not only based on the presence of SMEs among beneficiaries, but overall on actions to promote further industry involvement for the **full exploitation of PnD-related technological innovation and medical devices**. For instance, newly identified genes/markers could be microarrayed - or exploited with a yet unknown new technology - for phenotype and immunological characterization of PnD; potency markers could be commercialized for the assessment of different cell preparations; GMP protocols could lead to off-the-shelf products.

3.1. Description of the Work Plan

3.1.1. Description of Working Groups

The WGs are organized based on the main aims of this Action (described in Section 1.2.1). Each WG is represented by participants who are actively carrying out in vitro and preclinical studies, veterinary medicine, clinical trials, and regulatory aspects, that will contribute to the specific WG aims and deliverables. WGs will streamline efforts not only in that specific area, but on a larger scale, all WGs will work together to improve the clinical implementation of PnD.
Participants will associate into smaller collaborative groups, led by the Working Group Leaders (WGL) and Task Leaders (TL) on the basis of common interests (e.g. Pn tissue, cell population, technology, pre-clinical model, pathological condition) in order to contribute to the WG deliverables.
NB: **Participant research activities will not be carried out with COST funds.**
WG interaction is also represented by the recurrent tasks listed below:

- Provide an updated list of expertise, capacities, materials and technologies to the network;
- Review and update state-of-the-art development on the topic of interest;
- Contribute to the network-wide register of capabilities available to the scientific community;
- Contribute to the website contents;
- Contribute to the organization and implementation of events and training activities;
- Contribute to the strategy for the development of clinical trials;
- Contribute to management through progress reports.

WG1. IN VITRO CHARACTERIZATION AND CONSENSUS

NEED: Over the past decade, in vitro research on PnD has exponentially increased. The literature is a rich reservoir of these findings, but often misinterpretations lead to confusion, redundancy, and inconsistency. Protocols and biological materials need to be exchanged in order to compare results and reach a general consensus on the in vitro methods used to characterize PnD, and the expected results. Ideally, reference labs who are experts for different types of analyses, such as flow cytometry, differentiation, and immunomodulation, should be identified. This, along with the exchange of materials, should allow for characterization and harmonization of procedures. This WG will deliver robust and standardized protocols that will serve as a pillar for all other WGs.
AIMS: 1) To establish reference nomenclature for Pn cells from different placental regions and their bioactive molecules; **2)** To define standards for the preparation and cryopreservation of Pn cells from different placental regions and their bioactive molecules; **3)** To define standards for in vitro characterization of Pn cells from different placental regions and their bioactive molecules.
TASKS/ACTIVITIES:

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T1.1. An online questionnaire will be prepared and completed by each participant to establish the baseline regarding Pn compartment, cells, and/or bioactive molecules of interest, nomenclature, protocols used, and tests implemented for in vitro characterization. Workflows and accompanying documents will be prepared to establish a network-wide exchange of PnD for research purposes and comparison of protocols and outcomes;
T1.2. Analysis and comparison of protocols:

- Collection and shipping of PnD;
- Ultrastructural and immunohistochemical/phenotype characterization of Pn cells in situ;
- Isolation and culture of different Pn cells;
- Phenotype and functional characterization of isolated Pn cells (immunomodulatory properties, differentiation, bioactive molecules produced);
- Preparation and functional characterization of bioactive molecules produced by Pn cells;
- Cryopreservation of PnD.

T1.3. Develop and promote the implementation of standard operating procedures (SOP) for the steps listed in T1.2. This task will be fed by results obtained from T1.2 and will collaborate with T5.2.
DELIVERABLES:
D1a. Completion of the "In Vitro" section of the network register (D6d) for available PnD, tests for isolation, characterization, and cryopreservation (M4, updates and M47).
D1b. Consensus nomenclature for cells from different Pn compartments (M12).
D1c. "Online PnD atlas": informative maps of placental regions and cell populations which can be isolated from each (M12 and updates).
D1d. Peer-reviewed publication of standardized protocols for: (i) collection, cryopreservation, and shipping of Pn tissues and on the definition of characteristics of Pn cells in situ; (ii) isolation, culture and in vitro methods to characterize cells isolated from different placental regions; (iii) in vitro methods to prepare and characterize derivatives from cells from different placental regions (M46).
MILESTONES:
M1a. Meeting to reach consensus on the methodology to compare and standardize protocols (M4).
M1b-g. Protocol comparison update WG1 meetings (M12,M18,M24,M30,M36,M42).

WG2: PRECLINICAL STUDIES AND MODELS

NEED: There has been extensive research on the effects of PnD in animal models of acute injury and chronic diseases associated with inflammatory processes, and results have shown their beneficial effects. However, it is still unclear which cells and/or derivatives provide optimal results, which treatment regimen(s), and which mechanisms are involved. The presence of co-morbidities is an important issue often neglected in preclinical studies that needs to be taken into account in order to ensure relevant findings in terms of clinical translation. Within this WG, forces will be combined to compare results, identify research gaps, and implement networking strategies to answer open questions. A clear understanding of the therapeutic potential and underlying mechanisms will allow for the identification of which PnD could potentially provide the optimal results in different diseases in veterinary (WG3) and human medicine (WG4). This will provide rationale and research-based platform regarding the several potential uses of PnD.
AIMS: 1) To review studies in animal models in order to grade efficacy of therapeutic interventions and identify research gaps for each animal model and/or disease of interest; **2)** To develop new treatment modalities for pre-clinical studies relative to the identified research gaps and priorities that build upon the consensus or standardized protocols defined in WG1; **3)** To propose disease-specific therapeutic approaches using PnD based on their potential to differentiate into tissue-specific cells or to induce bystander effects through their secretome.
TASKS/ACTIVITIES:
T2.1. An online questionnaire will be prepared and completed by each participant to establish the baseline regarding animal models used and available to the network for studying PnD. Analysis and comparison of data from the questionnaires and published and unpublished results obtained from in vivo testing. Animal models, PnD, and treatment regimens used will be considered. The focus will be

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on the diseases which mostly benefit from the differentiation capabilities of perinatal cells into tissue-specific cells (e.g. reconstruction of vascular/cartilage/liver defects) or from their paracrine effects (e.g. inflammatory diseases). The inclusion of critical research questions and recommendations will be of high importance for the further development of therapeutic approaches in pre-clinical animal models and clinical application in human disease (WG4).
T2.2. Develop consensual methodological workflows, including the vitro methods from WG1, to support the therapeutic claims in each of the studies analyzed in T2.1, especially in regards to mechanisms of action (i.e. differentiation of Pn cells or paracrine effects).
DELIVERABLES:
D2a. Completion of the "In Vivo" section of the network register (D6d) for available animal models treated with PnD, references, and experts (M4, updates and M47).
D2b. Multi-author review regarding consensus on disease-specific therapeutic protocols and PnD to be used, dosage, and route of administration, and standardized readouts, pin-pointing research gaps to advance the research as well as to pave the way for human clinical application(s) (M30).
D2c. Multi-author review and position paper on mechanism(s) of action for therapeutic interventions, and suggestions for disease-specific therapeutic approaches (M46).
MILESTONES:
M2a. WG2 meeting to reach a consensus on methodology and to compare results, identify research gaps and mechanisms that characterize efficacy of PnD in similar diseases (M4).
M2b-g. Update meetings for comparative analysis of in vivo studies (M12,M18,M24,M30,M36,M42).

WG3: VETERINARY MEDICINE

NEED: Promising therapeutic approaches in veterinary medicine have been developed using mesenchymal stem cells (MSC). More recently, the use of Pn cells has provided encouraging results, however often only in single case studies or sporadic cases. There is a relevant need to form a network of veterinarians in order to identify treatable, compare previous and ongoing therapeutic results, and to shed light into the possible mechanisms of action. Veterinary medicine is often seen as stand-alone; the advocates believe that this WG is an essential part of the Action and will be precious in bridging the in vitro (WG1) and preclinical (WG2) work to applications in humans (WG4).
AIMS: **1)** To gather clinical and follow-up data from case reports to gain a better understanding of the outcomes; **2)** To build upon WG2's findings to investigate the mechanisms underlying the therapeutic effects of PnD in veterinary clinic for companion and large animals, in order to identify disease-specific therapeutic approaches, and provide insight for the applications in humans (WG4).
TASKS/ACTIVITIES:
T3.1. An online questionnaire will be prepared and completed by each participant to establish the baseline regarding diseases treated in animals and PnD used. A multi-disciplinary analysis of the worldwide state-of-the-art regarding the safety and therapeutic potential of PnD will be performed.
T3.2. Develop a consensus on methodological workflows, including the vitro methods from WG1, that should be applied to support the therapeutic claims in each of the studies analyzed in T3.1.
DELIVERABLES:
D3a. Completion of the "Veterinary medicine" section of the network register (D6d) for disease- and species-specific therapeutic approach versus PnD used, dosage, and route of administration (M10, updates and M47).
D3b. Publication of a review and position paper of the worldwide state-of-the-art and on innovative PnD-based therapies in veterinary medicine, including recommendations for the development of therapeutic approaches using PnD, and implications on clinical application in human disease (M40).
MILESTONES:
M3a. WG3 meeting to reach a consensus on methodology for veterinary trials/case studies comparison (M4).
M3b-d. Update meetings for comparative analysis of veterinarian medicine (M12,M22,M32).

WG4: CLINICAL APPLICATIONS

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NEED: A variety of PnD have been investigated in regenerative medicine, but their translation into clinical practice has been, to date, haphazard, incomplete and slow, ultimately limiting their therapeutic potential. To improve chances of transforming patient outcome, the need is to understand the potential clinical applications of PnD and identify diseases to consider PnD as first- and second-line treatment. WG4 builds upon WG1, 2, and 3 findings, driving the Action's vision to bring effective, novel, PnD-based therapies to patients.

AIMS: 1) To foster networking between researchers and clinicians, from both academia and industry, who perform clinical trials using PnD to:

a. Consider current tissue engineering and paracrine strategies and develop new and/or improved clinical pathways to deliver PnD to patients for better therapeutic outcomes;
b. Support the development of critical regulatory aspects of PnD to achieve successful clinical translation (WG5).

TASKS/ACTIVITIES:

T4.1 An online questionnaire will be completed by each participant to establish the baseline regarding patients, stakeholders, PnD used, and data available to the network. Individual groups will consider how PnD could be used for therapeutic approaches through analysis and comparison of outcomes. Studies will focus on regenerative approaches (e.g. cell pre-differentiation, scaffolds, tissue engineering technologies for different anatomic compartments) and regenerative medicine approaches (e.g. paracrine acting molecules, nanovectors, administration route).

DELIVERABLES:

D4a. Completion of the "Clinical" part of the network register (D6d) for diseases and their potential therapeutic approaches in terms of PnD used, dosage, and route of administration (M10, updates and M47).

D4b. Clinical review manuscript on the use of different PnD in patients (M40).

MILESTONES:

M4a. WG4 meeting to discuss and compare clinical trials and results, and PnD used, and to discuss obstacles/problems/limitations, drawbacks, how to improve trials, and positive and negative results of ongoing trials (M6).

M4b-d. Update meetings to evaluate results from WG1, WG2, and WG3 and their influence on improving the quality of clinical trials and the description of critical needs and recommendations for regulatory aspects (M12, M24, M36).

WG5: REGULATORY AND ETHICAL ASPECTS

NEED: There is an ever-increasing need for clinicians and researchers to produce PnD in a regulated environment, which ensures quality and safety as well as durable investments. Regulatory agencies are confronted with new therapies and have to make clear and concise decisions and regulations. The need is to define specific regulatory processes and standards. In addition, to overcome social and ethical concerns about the use of PnD for certain diseases, it is essential to consider the European patients' perspective while maintaining quality and safety of investigational therapies. This WG will provide a basis for cooperative work between clinicians related patient associations and competent authorities on the PnD areas of interest.

AIMS: 1) To discuss general regulatory issues and specific exemptions for PnD; **2)** To set commonly accepted GMP and regulatory standards; **3)** To provide an understanding on patient perspectives concerning the collection and use PnD; **4)** To discuss with stakeholders, including regulatory agencies, ethical issues for donation, processing and use of Pn tissues; **5)** To guide clinicians for optimal clinical trial design and the successful implementation of efficient and safe clinical trials.

TASKS/ACTIVITIES:

T5.1 An online questionnaire will be completed by clinicians and regulators to establish the base-line, including the known status on preclinical and trial data. An evaluation of relevant information in regards to existing and draft versions of European Standards will be performed;

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T5.2 Develop specific regulatory standards as common practice for donation, processing, microbiological testing, stability, product characterization, transport and therapeutic use of PnD. This task will collaborate with T1.3.
T5.3 Establish a consensus on methods for PnD accepted as reference in the GMP setting;
T5.4 Define awareness, availability, cost-efficiency and clinical effectiveness as well as sustainability for GMP-grade PnD products;
T5.5 Review the current European patient perspectives on the collection and use of bio-banking and therapeutic purposes, for the selected diseases. Development of patient surveys to fill any gaps on views, including ethical concerns, that are critical for successful clinical translation. Debate with all stakeholders of PnD-related ethical issues. This will improve the chances of ethical approval of future trials.
T.5.6 Harmonize duties and needs of R&D, manufacturer, clinicians, regulators and patients of PnD products
DELIVERABLES:
D5a. European Standards for QC and QA of clinical-grade PnD (M18).
D5b. Standard SOPs for GMP-grade validation, qualification and testing PnD (M24).
D5c. Review of EU stakeholder's and patient's views on the collection and use of PnD for therapeutic approaches (M36).
D5d. Sustainability model for a PnD product (M42)
MILESTONES:
M5a-c. Update meetings on standards development, and stakeholder's and patient's view (M12,M30,M42)

WG6. DISSEMINATION AND EXPLOITATION

NEED: The Action will generate a wide variety of knowledge. To guarantee maximum impact, it is essential to convoy this information toward target groups through appropriate channels and tools. This will be of interest for scientific and medical communities, and could be exploited for industrial and clinical applications. It will be used for educational purposes, for students, patients, and public.
AIMS: 1) Create a dynamic and favourable "PnD-related environment" in order to promote research, encourage the creation and use of standardized protocols, favour innovative therapeutics; **2)** Address the main research-related stakeholders (scientific/medical communities, students, industry) and promote return actions (e.g. MD/PhD thesis, IP exploitation agreements); **3)** Debate ethical and acceptance issues with the public and patients.
TASKS:
T6.1 Cooperation with selected established scientific societies;
T6.2 Development of training tools for medical and biomedical students;
T6.3 Technology transfer towards the biomedical industry for human and veterinary clinics by e.g. public-private co-development of knowledge, skills and processes, personnel secondments, exploitation agreements;
T6.4 Fully confront science issues and their ethical concerns beyond the scientific and medical communities.
DELIVERABLES:
D6a Yearly Dissemination and Exploitation plans (M3, M15, M27, M39).
D6b Website published (M3).
D6c Flyers for mothers-to-be to create awareness and encourage donation (M4).
D6d Publication of the network-wide register of capacities (M8).
D6e Opening of the "Business opportunities" section of the website (M11 and updates).
D6f Training tools for medical, biomedical, and science students (M15).
MILESTONES:
M6a 1st European Summer/Winter School (M12).
M6b 2nd European Summer/Winter School (M36).
M6c 1st edition of the "European day in the PnD lab" for biomedical students (M24).
M6d 2nd edition of the "European day in the PnD lab" for biomedical students (M35).

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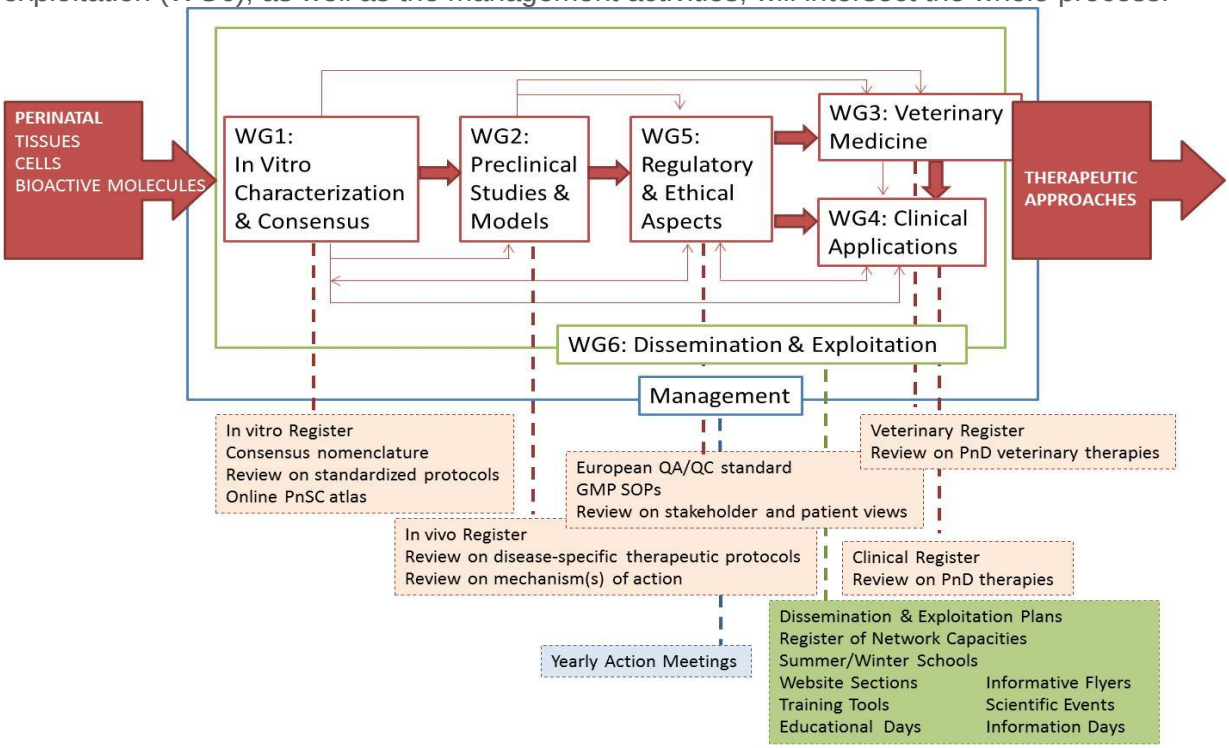
M6e The “PnD European information day” for Patient associations and layman (M16).
M6f European Workshop “Science & Industry” (M36).
M6g 1st Pn tissues and derivatives European Conference (M24).
M6h 2nd Pn tissue and derivatives European Conference (M46).

3.1.2. GANTT Diagram

year	1				2				3				4			
month	*6*			*12*	*18*			*24*	*30*			*36*	*42*			*48*
WG1. IN VITRO CHARACTERIZATION AND CONSENSUS	D1a M1a		D1b/D1c	M1b	M1c			M1d	M1e			M2f	M1g		D1d	D1a
WG2: PRECLINICAL STUDIES AND MODELS	D2a M2a			M2b	M2c			M2d	D2b M2e			M2f	M2g		D2c	D2a
WG3: VETERINARY MEDICINE	M3a		D3a	M3b			M3c			M3d			D3b			D3a
WG4: CLINICAL APPLICATIONS		M4a	D4a	M4b				M4c				M4d	D4b		D4a	
WG5: REGULATORY AND ETHICAL ASPECTS				M5a	D5a			D5b		M5b		D5c	D5d M5c			
WG6. DISSEMINATION AND EXPLOITATION			D6a/D6b D6c D6d D6 M6a		D6a/D6f M6e			M6c/M6g	D6a			M6d M6b/M6f	D6a		M6h	
MANAGEMENT	MMa			MMb				MMc				MMd				MMe/MMf

3.1.3. PERT Chart (optional)

The Action’s final goal is to streamline the flow from basic research to clinical application of PnD. Each WG will contribute to the inter-WG flow with pertinent activities and specific deliverables. In order to follow the clinical research developmental progression, in vitro (WG1) and in vivo (WG2) studies will feed all downstream WGs, while the regulatory and ethical research (WG5) is pivotal between the in vitro (WG1), in vivo (WG2), and clinical (WG4) studies. Veterinary clinics will receive input from all upstream WGs and provide input for clinical applications (WG4). Dissemination and exploitation (WG6), as well as the management activities, will intersect the whole process.



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3.1.4. Risk and Contingency Plans

The **major risks identified** are related to the efficient management of such of a large network, and the capacity to attract external funds to ensure the translation of PnD from bench to bedside.
Difficulty in coordinating large and multidisciplinary Working Groups. NATAL has set a clear management structure, with well-defined management bodies and roles, and governance. To implement this plan, the Action chair and the Grant holder will have proven excellent technical and financial capacity, respectively, and strong experience in large-scale project management.
Inaccurate budget allocation. The MC will identify necessary re-allocations among participants and/or between cost categories, and define a budget redistribution.
Delayed delivery of deliverables. The fine planning and coordination of task activities could be managed not only by the Working Group Leaders (WGL) but also by additional Task Leaders. In case of work load underestimation, the Management Committee (MC) could reinforce the working team with additional participants.
Conflicts regarding knowledge use and exploitation. The IPR team will oversee IP management across all WGs and, with the support of legal offices of individual teams, will clear agreements and contracts.
Difficulty in executing research and innovation activities with own funds. Although single research and innovation projects will be financed with other funds than those provided by the Action, the networking activities of the Action offer the possibility to create competitive partnerships for European grants (e.g. H2020, EMBO) and private foundations for specific diseases, to coordinate clinical trials for interested sponsors, and to implement industry-research partnerships for translational and technological outputs.
Attract industry investments for economic sustainability of PnD-based therapies. The Action is designed to stimulate private investments, such as through the active participation of companies to the WGs activities and the dedicated "Science & Industry" workshop. If these initiatives will not be sufficient, the Action could implement other strategies, such as the promotion or arrangement for the network proposers to attend international business angels meetings and to participate to SME-academia matchmaking events organised by European projects/initiatives/showcases (e.g. *Investing in Medical Innovations Fair; Fit For Health 2.0)*.
Knowledge gap to clinical translation. PnD are a variety of entities that, despite common origin (i.e. placenta), have unique features. Some of them have extensively been characterized and are being clinically tested in a specific pathology. Others will be fully investigated for their therapeutic potential and underlying mechanisms during the Action, until they are ready to move forward in the translational process.

3.2. Management structures and procedures

a. Management bodies and governance will be set accordingly to "Rules of Procedure for Management Committee" (Annex I).
Management Committee (MC). It will be composed of up to two representatives from each Member/Cooperating State participating in the Action, plus up to two representatives from Near Neighbour Countries or International Partner Countries. The MC has decisional power. It will meet once a year and have conference calls once a year. MC will be in charge of:

- *Election of the Action Chair* (responsible for coordinating MC activities), Vice-Chair, Grant Holder, and 6 Working Group Leaders (WGL). A Task Leader could be elected if one or more tasks deem too large to be coordinated by the referring WGL.
- *Coordination of the Action*. The MC will be responsible for the overall strategy and structure of the Action, including the allocation of funds. The MC will solicit and approve a Work Plan for each WG and coordinate their interaction. WGL will have a joint remote conference or physical meeting every six months to ensure the harmonisation and cross-talk among WGs. To closely monitor the activities, each WG will report to the MC every three months. Participants will join one or more WGs according to their expertise and scientific interests, in agreement with the MC.
- *Financial management*. The MC will decide which participants qualify for reimbursement.
- *Reporting*. MC will perform the reporting duties allowing for the technical and financial monitoring and assessment of the Action. The MC will review and approve the reports of the WGs. The MC

will monitor the progress of the Action, in accordance to the Technical Annex. In order to avoid delays, WGs will send to the MC a short report every three months.

- *Establish specific provisions* linked to the management, share, creation, dissemination or exploitation of knowledge, including Public webpage policy and management of Intellectual Property. These provisions shall comply with international legislation and the need for protecting the participants' legitimate interests.

Steering Committee (SC). The Action Chair, Vice-Chair and the six WG leaders will constitute the Steering Committee. The SC will be responsible for the daily management and general organization of the Action. The SC will have executive power in implementing the decisions of the MC. The SC will meet at least once a year and will have additional meetings through internet/teleconferences when necessary.

Additional Bodies. Specific working teams and coordinators will be elected by the MC to manage the implementation of specific activities. Each team will implement the decisions of the MC.

- IPR Team to manage the knowledge outputs and their exploitation and translation (3 people);
- Content Team for online tools: website, atlas, and network register (6 people);
- Survey Team for PnD collection centres (3 people);
- Day in the Lab team (3 people);
- Three Workshop/Conference organizing teams of 3 people each;
- Two Summer/Winter School organizing teams of 3 people each.

b. Scientific Advisory Board (SAB)

Considering the Action's goal to promote the clinical development of PnD and its ambition to become an European reference point for PnD research, an external and independent Scientific Advisory Board (SAB) has been nominated. The SAB is composed of 1 Australian and 4 European renowned experts endorsing the Action. They are scholars in the field of immunology, regulatory affairs for cell-based products, or clinical trials with MSC transplantation. They will annually review, evaluate and report to the MC on the Action's activities, outputs, dissemination and exploitation plans, allowing the Action to receive an external, unbiased assessment of its progress.

c. Meetings

The Kick-off Meeting will be held within the first month. Yearly general project meetings will be organized. Whenever possible, these meetings will be held back to back with an event organized by the Action (e.g. Summer School, Congress), improving interactions and reducing travel costs.

The MC, SC, and WG meetings will be organized in the same dates, spanning 1-2 days with non-overlapping schedules, favouring the participation of the members of the Action.

Management Milestones:

YEAR 1: **MMa** Kick off Meeting (M1)
MMb 1st Project Meeting (M12 joint with 1st European Summer/Winter School)
YEAR 2: **MMc** 2nd Project Meeting (M24, joint with 1st European Conference)
YEAR 3: **MMd** 3rd Project Meeting (M36 joint with Workshop "Science & Industry") and 2nd European Summer/Winter School)
YEAR 4: **MMe** 4th Project Meeting (M46 joint with 2nd European Conference)
MMf Formal engagement for the durability of the network and (online) outputs, beyond NATAL's life (M46)

d. Sustainability and durability of the Action

Sustainability. The Action participants are well aware that funds are needed to sustain the research plans and activities set in the WGs, beyond the COST contribution for the networking activities. As all of them have public, national, and international, and/or private funds to finance their research activities, the participants will apply for funds also in the future. The Action will be an opportunity to jointly apply for European transnational programs for research grants, and to reach the private investors, not only those companies participating to the Action, but especially the Biotech Industry tanks to the "Science & Industry" workshop organised at M36 and the "business opportunities" dedicated part of the Action website.

Durability. During the Action final meeting, the MC Chair will ask a **formal engagement** of each Participant to insure the durability of the network, its outputs and online developed instruments, beyond NATAL's life.

3.3. Network as a whole

This network has been designed to become the reference point for research on PnD and, if funded, the Action will be the widest network on PnD. Non-EU members are also present with outstanding scientists and clinicians in the field, some of which are part of the collaborative U.S. cell manufacturing community which in 2016 have implemented a 10-year roadmap (strategy) combining focused research and development activities with initiatives to support and sustain the cell manufacturing industry. This close collaboration will also facilitate the implementation of technologies across cell manufacturing facilities, accelerating the time it takes for technologies to move from the laboratory to commercial scale.
Proposers features. This Action has attempted to bring all the European teams that have published on PnD in the past five to ten years. If successful, the network will open its doors to newcomers in the field. They represent an interdisciplinary team of 45 partners, including 33 Higher Education and associated Organizations, 7 Business Enterprises, 3 Private Non-Profit without market revenues, and 2 Government/Intergovernmental Organizations (except Higher Education).
Scientific expertise. The partnership gathers all complementary and necessary expertise to address the multidisciplinary research activities encompassed by the Action's program. They have an array of broad interests including immunology and reproductive immunology, regenerative medicine, biotechnology/nanobiotechnology, genetic engineering and cell reprogramming, fetal and neonatal gene transfer and therapeutic approaches for a variety of congenital malformations and diseases.
Bio-medical business. The 7 SMEs core business include bio-banking (2), cell therapy/regenerative medicine related products (3), in vitro research products (1), and processing equipment (1).
Capacity and skills. The proponents have a strong track record in experimental design and strategies, grant application, large collaborative project management, knowledge and IPR management, regulatory affairs, technology transfer, clinical translation, business development and contribution to public awareness of science. The administrative, legal, and international research offices of their institutions provide additional capacity to the Action.
Geographic distribution and international cooperation. This Action brings together all leading and emerging teams from 16 COST Country Institutions, 1 Near Neighbour Country, and 7 International Partners.
Additional Partners. The flexibility of the NATAL framework will **assure the incorporation of emerging issues and the integration of new parties.** NATAL will allow the participation of researchers, engineers, and scholars from European and non-European countries, with the aim to foster the dialogue and cooperation with key actors in the European and global science and technology on the basis of ascertained mutual benefit. The integration of new Partners will be subject to the consent of the Management Committee.