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Short Report

Promoting the ethical use of safe and effective cell-based products: the Andalusian plan on regenerative medicine



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ABSTRACT

With regard to regenerative medicine, the expectations generated over the last two decades and the time involved in developing this type of therapies, together with the availability of devices that allow point-of-care treatments through the rapid isolation of cellular or plasma products from patients in the operating theater, represent the perfect breeding ground for the offering of unproven or unregulated therapies on a global scale. A multidisciplinary approach—one based on the collaboration of institutions that, from the perspective of their area of competence, can contribute to reversing this worrying situation—to this problem is essential. It is a priority for local health authorities to take measures that are adapted to the particular situation and regulatory framework of their respective territory. In this article, the authors present the regenerative medicine action plan promoted by the Andalusian Transplant Coordination (i.e., the action plan for the largest region in Spain), highlighting the aspects the authors believe are fundamental to its success. The authors describe, in summary form, the methodology, phases of the plan, actions designed, key collaborators, important milestones achieved and main lessons they have drawn from their experience so that this can serve as an example for other institutions interested in promoting the ethical use of this type of therapy.

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Introduction

Regenerative medicine seeks to replace or regenerate cells, tissues and organs of the human body to repair or improve their functioning [1]. This is not a new field of medicine, as the first successful tissue transplant, that of a cornea, was performed more than a century ago [2], and in the 1950s the first successful kidney [3] and bone marrow [4] transplants were performed.

However, we are currently witnessing the emergence of new technologies and innovative therapies based on genetic material, cells and other biological products of human origin, such as plasma, which represent a revolution in regenerative medicine [5]. In fact, research in this field has grown exponentially in recent years, and promising results have been published on pathologies of all kinds, whether related to aging, lifestyle, traumatic injury, genetic alteration or tumor-related disease [6].

Specifically, in the field of so-called advanced therapies, such as cell therapy, tissue engineering or gene therapy, the number of clinical trials has continued to grow over the last decade, exceeding 1,000 trials worldwide in 2019 [7]. However, the number of therapies that

has been authorized by regulatory agencies for application to patients outside clinical trials is still very small [8] given the complexity of therapy development due not only to purely scientific and technical aspects but also to regulatory ones [9,10].

By contrast, the growing supply of biological therapies that lack scientific evidence or are offered outside the regulatory framework of various countries represents a recognized phenomenon [11,12]. The boom in businesses offering cell-based treatments, whether stem cell or otherwise, and platelet-enriched plasma (PRP) has been favored by the introduction to the market of devices that allow these biological products to be easily obtained from the patient's own tissues and blood and administered during the same procedure, as point-of-care therapies, often without all the required authorizations [13].

In view of this situation, it is important that all entities that play a role in this field collaborate, within the scope of their competencies and capabilities, to fight against this type of situation and promote the correct use of these therapies while facilitating patient access to safe and effective therapies. In this article, the authors present, in summary form, the action plan in regenerative medicine promoted by the Andalusian Transplant Coordination, highlighting the aspects we believe to be fundamental for its success, with the aim that it serve as a model for other institutions interested in promoting the ethical use of this type of therapy.

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The Andalusian Transplant Coordination [14] is a governmental entity within the regional health care system of Andalusia that represents the competent authority for cell, tissue and organ donation and transplantation activities in Andalusia, which is the largest region in Spain, with 8.5 million inhabitants. Among other responsibilities, the Andalusian Transplant Coordination is responsible for the organization of these activities as well as the authorization of centers, including those in which cells and tissues are harvested for manufacturing cell and gene therapies; it is not responsible for authorization of the manufacture, research and marketing of medicinal products. This governmental entity directs the Andalusian network of transplant coordinators located in public and private hospitals and facilitates support for donation and transplantation activities.

Regulatory framework applying to cell-based products and PRP

The regulations governing the manufacture and application of biological products of human origin, and especially those obtained from cells, are complex [15–17] and not always well known by the professionals who prescribe or administer these treatments. In brief, cell- and tissue-based products subjected to substantial manipulation or not intended to be used for the same essential function are classified as advanced therapy medicinal products (ATMPs) in the European Union (EU). The European Regulation 1394/2007 on ATMPs [18], mandatory for all EU countries, establishes a centralized marketing authorization procedure for these medicinal products when they are intended to be placed on the market.

Cell- and tissue-based products that are not substantially manipulated and intended to be used for the same essential function are usually considered cell or tissue transplants, as in the case of hematopoietic stem cell transplantation; or they are considered transfusion medicine, as in the case of adoptive cellular immunotherapy to prevent relapse in patients with leukemia who are infused with donor lymphocytes. Donation, procurement, testing, processing, preservation, storage, distribution, traceability and coding of human tissues and cells for transplantation have to comply with the requirements and standards of quality and safety set out in several European directives [19–22]. Similarly, collection, testing, processing, storage, distribution and traceability of human blood and blood components for transfusion have to comply with standards of quality and safety regulated at the European level [23–25].

In the case of ATMPs using cells, tissues, human blood or blood components as starting materials, the same European legislation is applicable for their donation, procurement or collection, testing, traceability and coding [18,26]. Concerning the requirements for processing ATMPs, Good Manufacturing Practice-compliant facilities are required, and the principles of Good Manufacturing Practice should be followed [27], especially those specific to ATMPs [28]. The clinical use of ATMPs must follow the Regulation 536/2014 on clinical trials [29]—when ATMPs are still considered investigational medicinal products—or they have to be granted marketing authorization by the European Commission via a centralized procedure, as mentioned previously. Spain, as a member of the EU, regulates ATMPs, cell and tissue transplants and transfusion medicine according to EU legislation.

Related to the regulation of PRP, platelet concentrates may fall within different national legal frameworks in the EU for which the appropriate quality, safety and vigilance requirements need to be applied (these may include requirements for blood, tissues and cells, and medicinal products) [30]. In Spain, PRP is regulated as a medicinal product that, in the specific case of autologous PRP, is considered a non-industrially manufactured medicine to meet special needs [31].

Detailed information regarding Spanish regulation of biological products of human origin [13] is outside the scope of this article. In any case, advertising these products is forbidden. It also should be

noted that the use of unproven ATMPs (outside clinical trials or compassionate use) is not legal in Spain.

Rationale and objective

As many of these products are at least partially regulated by the legislation on cell and tissue donation for transplantation, the Andalusian Transplant Coordination, in 2019, designed and launched an action plan in regenerative medicine. Nevertheless, the transplant coordination is only responsible for the donation activities of human cells and tissues, not for manufacturing, research and marketing of medicinal products.

Consequently, the main objective of the plan is to contribute to improving the knowledge of professionals and patients regarding the use of biological therapies (mainly cell therapy and PRP) in the field of regenerative medicine and the legal requirements for their administration, with the maximum guarantees of quality, safety and effectiveness. The Andalusian Transplant Coordination serves an exclusively advisory role, working with professional associations, scientific societies, health center inspectors, health center directors and patient associations, and establishes coordination mechanisms with the different agents involved.

The professionals and entities to which the plan is directed also include those working in the development of these therapies, whether in public or private institutions. The plan is intended to assist them in the procedure for authorizing the procurement of human tissues and cells and to support them in complying with the legal requirements governing donation, coding, traceability and notification activities. In some cases, help is also given with logistical aspects related to the procurement and shipping of tissues and cells from the donor center to the manufacturing laboratory and the subsequent shipping of the manufactured products to the hospital where they are to be administered [32].

Methods

The plan covers an initial period of 3 years: 2019–2021. However, the plan has been drawn up within the framework of the Plan, Do, Check, Act cycle methodology of continuous improvement [33]. Therefore, the duration could be extended depending on the results achieved in the initial 3-year period.

The activities planned are included in the following 5 phases: (i) situation analysis, (ii) development of technical and informative material, (iii) information and dissemination, (iv) intervention and (v) evaluation. These phases are not strictly consecutive, as some may be carried out simultaneously. Figure 1 shows these phases within the corresponding phase of the Plan, Do, Check, Act cycle. The breakdown of the activities defined within each phase is summarized in Figure 2.

Key agents

In Spain, in collaboration with health inspectors, the regional health ministries are responsible for authorization and accreditation of health centers to verify compliance with legal requirements. However, the professional licensing bodies are the Spanish ministries of education and health, and professional associations play a role in the accreditation of practitioners and other health professionals.

Based on the premise that the Andalusian Transplant Coordination has a limited scope of competence and that its greatest contribution should be acting as a facilitator and advisor to many of the agents involved in the development and application of these therapies, the designed plan pivots on establishing coordination mechanisms with those agents involved from the development to application of these therapies, including regulators, prescribers, health managers, inspectors and patients. In this sense, from the beginning, the transplant coordination identified the key agents for

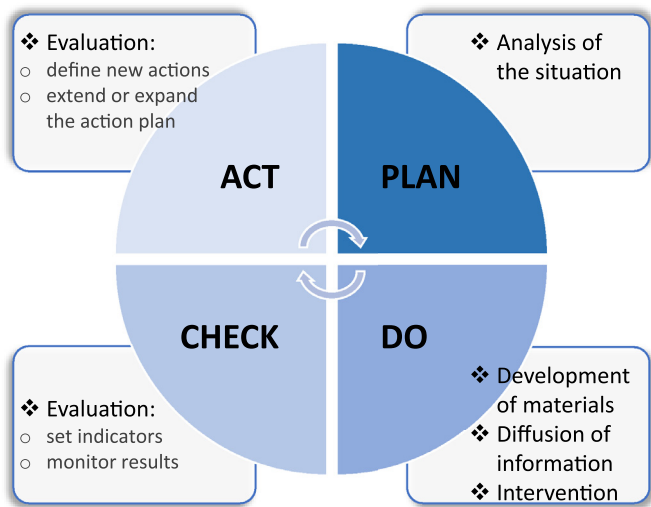


Figure 1. Phases of the Andalusian Transplant Coordination regenerative medicine action plan within the framework of the PDCA cycle. PDCA, Plan, Do, Check, Act. (Color version of figure is available online).

the execution of the plan, whose collaboration is essential, and classified them as internal or external agents, depending on whether their scope of action is limited to Andalusia (Table 1).

Among the main internal players, there are five the Andalusian Transplant Coordination considers key. One of the most relevant is the professional associations that bring together the main prescribers and professionals who administer these therapies, including doctors, dentists, physiotherapists, podiatrists and nurses. Also key are the scientific societies, especially those of the clinical specialties in which these treatments are most frequently applied as point-of-care treatments through a procedure that encompasses everything from obtaining tissue and blood from patients to processing until administration. Among these scientific societies are the societies of sports medicine, orthopedic surgery and traumatology, aesthetic medicine, dermatology, dentistry, plastic surgery, maxillofacial surgery, oral surgery, general surgery and ophthalmology.

The manufacturers of advanced therapies, as well as the sponsors of clinical development, are also key in contributing to the appropriate use of these therapies. Likewise, the health authorities and managers of both public and private institutions are essential when implementing a plan with these characteristics. Managers include not only the management teams of hospitals and clinics but also those of institutions linked to this field, such as transfusion medicine centers and tissue banks. Of particular importance is the backing role of politicians responsible for the health system. Health center inspectors, who are also included in the group of health authorities, are noteworthy because they represent perhaps the most relevant key internal agent for achieving the objectives of a plan of this nature.

With regard to the key agents that are not part of the regional scope, the regulatory agencies stand out. In our case the most important agencies are the Agencia Española de Medicamentos y Productos Sanitarios (AEMPS) (i.e., the Spanish Agency for Medicines and Healthcare Products) and the Organización Nacional de Trasplantes (i.e., the National Transplant Organisation of Spain). Providing important support for a plan of these characteristics are the scientific societies that bring together, at an international level, researchers working on the generation of scientific evidence related to cell-based therapies and regenerative medicine. Patient associations, especially at the national level, are a fundamental and essential ally in reaching the plan's ultimate target. Given that the plan was created with the ambition of serving as a spearhead for an initiative that could extend beyond Andalusia's geographical boundaries, the transplant coordination understands that certain technical commissions of experts linked to the national health system represent another key agent.

Main milestones achieved

The main actions carried out in the first year since the launch of the regenerative medicine plan in June 2019 are grouped according to the first 4 phases of the plan: (i) situation analysis, (ii) development of technical and informative material, (iii) information and dissemination and (iv) intervention. With regard to situation analysis, all the planned actions have been completed (Figure 2). Streamlined communication with the health services inspectorate and the support received from those responsible for the Andalusian Health Service have been especially relevant.

In this first year, the Andalusian Transplant Coordination has prepared many materials of a technical and informative nature, including publishing an article in a national scientific journal [13], because the target audience is from within Spain and the regulations governing these therapies have specificities depending on the country. The main materials have been reviewed by AEMPS. As a result of the close collaboration established with the health services inspectorate, the transplant coordination has participated in the development of inspection protocols for clinics offering cell-based treatments. In addition, work has been done with the main sponsor of clinical trials of advanced therapies in Andalusia—an institution called the Andalusian Network for the Design and Translation of Advanced Therapies (formerly the Andalusian Initiative for Advanced Therapies)—and its network of medicine manufacturing laboratories to facilitate the implementation of the regulations on cell and tissue donation that apply to ATMPs. This work has consisted of preparing a technical document to facilitate compliance with the requirements for donor evaluation and coding as well as traceability and notification of serious adverse reactions and events, among others.

Within the phase of information and dissemination, planning meetings have been held with representatives of collaborating institutions belonging to the regional health ministry, such as the Andalusian Network of Transfusion Medicine, Tissues and Cells, and, in particular, with those of the health services inspectorate. In coordination with the latter, an important work meeting, which was the subject of a press release [34], was convened with representatives of professional associations and regional scientific societies. Thanks to their collaboration, it has been possible to disseminate information notes and technical documents among professional groups and clinical specialists. Information has also been disseminated to the management teams of all Andalusian Health Service hospitals and private clinics, who have been informed that, in the second half of this year, the health services inspectorate plans to visit centers offering regenerative medicine treatments.

The participation of the Andalusian Transplant Coordination in conferences of various scientific societies represents an instrumental dissemination activity, although the outbreak of the coronavirus pandemic has temporarily interrupted this activity. The most important action carried out in this field has been the organization of a course on inspection of tissue establishments and procurement and implant centers [35] geared toward inspectors. The program incorporated theoretical and practical content relating to the legal framework and current status of the use of cell-based therapies, whether stem cell or otherwise.

Through the participation of a member of the Andalusian Transplant Coordination in the International Society for Cell & Gene Therapy Presidential Task Force on the Use of Unproven and/or Unethical Cell and Gene Therapies, the transplant coordination is collaborating in the drawing up of informative documents aimed at multiple groups, especially patients [36], to help prevent them from undergoing treatments without sufficient guarantees of quality, safety and efficacy.

In relation to the interventions carried out, supporting and advising hospitals and clinics regarding their authorization as cell and tissue donation centers, prior to carrying out audits to obtain the corresponding authorization, is an activity that falls under the responsibility of the Andalusian Transplant Coordination and forms part of its normal

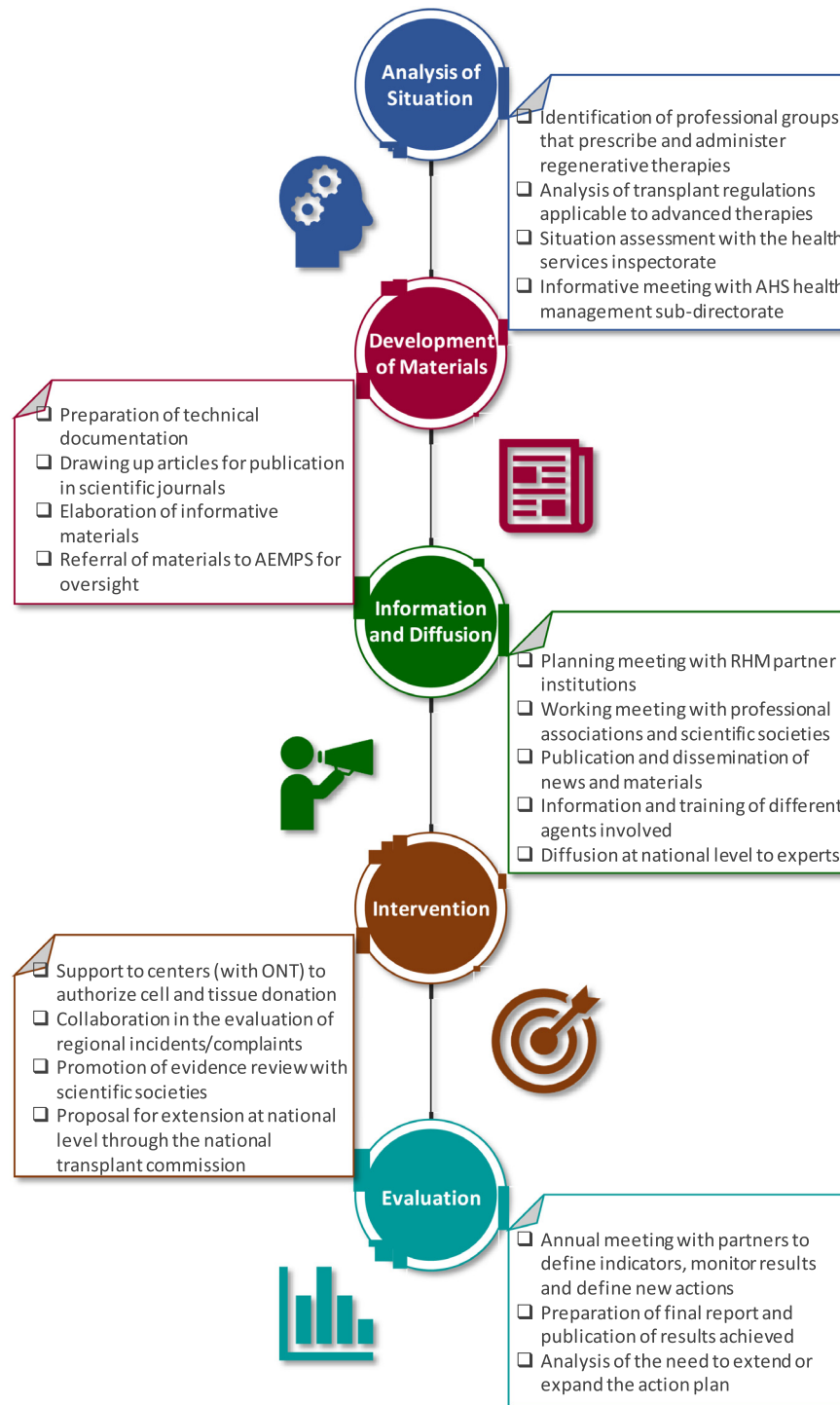


Figure 2. Main actions foreseen in the Andalusian Transplant Coordination regenerative medicine action plan. AEMPS, Agencia Española de Medicamentos y Productos Sanitarios (Spanish Agency for Medicines and Healthcare Products), AHS, Andalusian Health Service; ONT, Organización Nacional de Trasplantes; RHM, Regional Health Ministry. (Color version of figure is available online).

practice. In addition, collaboration with the health services inspectorate has been intensified, providing them with advice on the evaluation of regional incidents or complaints. One intervention envisaged in the plan is the promotion of the review of evidence of quality, safety and efficacy in each area of regenerative medicine by the corresponding regional scientific societies. Finally, the first steps have been taken to propose the extension of this initiative to other regions of Spain with the support of the Organización Nacional de Trasplantes through the transplant commission of the national health system.

Reflections and conclusions

The expectations generated over the last two decades in the field of stem cell research in particular and the field of regenerative medicine in general as well as the time involved in developing medicines, especially in this area, particularly complex from a scientific, technical and regulatory point of view, together with the growing introduction to the market of devices that allow point-of-care treatments through the rapid isolation of cellular or plasma products from

Table 1

Principal key agents for the development of the regenerative medicine plan in Andalusia.

Internal key agents	External key agents
Professional associations	Regulatory agencies
Clinical scientific societies	Scientific societies
Clinical trial sponsors and manufacturers of ATs	Patient associations
Health authorities and managers	Expert committees of the national health system
Health services inspection	

ATs, advanced therapies.

patients in the operating theater, represent the perfect breeding ground for the spread of these types of therapies around the world [37]. Frequently, unproven or unregulated therapies are offered, which means that patients are subjected, often unbeknownst to them, to interventions without necessary guarantees of quality, safety and effectiveness, underestimating the risks these therapies represent to their health [38]. Many organizations, from health organizations to scientific societies and regulatory agencies, are concerned about this situation [39–42].

From the authors' point of view, a multidisciplinary approach to this problem that is based on the collaboration of institutions that, from their area of competence, can contribute to reversing this worrying situation is essential. Although it is important to promote global initiatives and have the support of institutions such as the World Health Organization, it is a priority that local health authorities take measures adapted to the situation and regulatory framework of their own territory.

In this article, the authors have tried to explain the fundamental elements of the plan implemented by the Andalusian Transplant Coordination at the local level and would like to highlight some key issues. The authors believe that it is essential to improve the knowledge in scientific and legal aspects of regenerative medicine of health professionals, managers of health centers and health services inspectors. Moreover, any training or information action must be perfectly framed within the national regulatory framework and, therefore, supervised by the corresponding regulatory agencies. Since the transplant coordination started dissemination activities with materials supervised by AEMPS just 3 months ago, multiple calls have been received from public and private health care centers requesting additional information to carry out activities compliant with the Spanish legal framework.

However, the authors are aware that it is not always a question of lack of knowledge. Even though Spain has comprehensive legislation without regulatory gaps—not even in the case of devices for cell isolation at point of care [43]—there are companies that market this type of equipment (and clinics that use this equipment) using false or misleading legal and scientific arguments to convince people of the benefits of the interventions they offer because of the significant profits to be made. In these situations, the mere elaboration of recommendations is not enough, and coercive measures must be taken. Close cooperation with the health services inspectorate at the level of the Andalusian region is proving invaluable. Not only have the inspectors positively received the training that has been provided, especially given the complexity of the regulatory framework of these regenerative medicine practices, but they have also become the transplant coordination's main allies, or rather the transplant coordination has become theirs. This collaboration has had an immediate and direct effect. Several clinics have reported the cessation of some activities, and the only laboratory located in Andalusia that marketed point of care kits for the separation of mesenchymal cells has ceased its activity.

Finally, the authors believe it is important to contextualize the transplant coordination's action plan with regard to the characteristics of the

organization. This context is important to keep in mind when assessing the possible applicability to other organizations. As mentioned previously, Andalusia is the largest region in Spain, with 8.5 million inhabitants. In addition, Spain is one of the most decentralized European countries, which means that the health competencies of public health and health care fall on its different regions. On another note, the Andalusian Transplant Coordination is a governmental entity within the regional health care system, which in turn is part of the national health system—a public health system with universal coverage. In the authors' opinion, being part of a universal public health system, as well as having the support of the most senior health officials, is the main element facilitating the implementation of the plan. The authors hope that the possible extension of the plan to other regions of Spain will be facilitated by the coordination mechanisms of the national health system, which include technical commissions of experts, such as the national transplant commission, in which the regional transplant coordinators of the 17 regions of Spain participate.

In addition to the Andalusian Transplant Coordination, with limited competencies in this field, many organizations can contribute to improving the knowledge of professionals and patients as well as to promoting the ethical use of cell-based products. In the authors' experience, engagement with drug authorities, scientific and professional organizations and senior health officials, especially health inspectors, is crucial. In short, given the complexity of regenerative medicine, it is necessary to carry out, in collaboration with the multiple agents involved, a continuous evaluation of each of the phases so that difficulties and possible irregularities can be detected and actions to remedy them designed and implemented in accordance with the specific characteristics of each geographical area.

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The authors have no commercial, proprietary or financial interest in the products or companies described in this article.

Author Contributions

Conception and design of the study: Cuende N and Pérez-Villares JM. Acquisition of data: all authors. Analysis and interpretation of data: all authors. Drafting or revising the manuscript: Cuende N, Pérez-Villares JM, Álvarez-Márquez AJ and Díaz-Aunión C. All authors have approved the final article.

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