IP 1 (Nombre y apellidos)**:** DAVID EPSTEIN

TITLE OF THE PROJECT (ACRONYM): Cost-Effectiveness of Advanced Therapy Medicinal Products (CEAT)

SUMMARY

Background: The overall aim of this project is to undertake theoretical work and empirical studies related to the economic evaluation of a novel class of health technologies known as Advanced Therapy Medicinal Products (ATMP). These include gene therapy, cell therapy and regenerative medicine. ATMP are used to treat rare diseases, sometimes offering a cure for patients who cannot be treated in any other way. However, many fail to break through into commercial success, representing a waste of research resources, and those that do often charge extremely high prices.

Objectives: The objectives of the project are 1) Establish working guidelines for investment decisions (go/no go) by private and public investors in these therapies at distinct points in the life cycle 2) Recommend clear, consensual and practical criteria that decision makers in the national health service can use for establishing the price of such therapies and whether they should be financed in the NHS 3) Consider the theoretical and practical merits of distinct options for how such therapies might be reimbursed, for example, through risk-sharing schemes.

Methods: The project consists of six work packages (WP). WP1 reviews previous work in these areas and retrospectively identifies reasons for previous successes and failures. WP2 undertakes structured qualitative work with stakeholders to establish the specific challenges of translating the current R&D pipeline in ATMP into commercial success. Building on WP1 and 2, WP3 establishes coherent, pragmatic and workable methods and criteria for evaluating cost-effectiveness, social impact, degree of innovation, social return on investment, and pricing and reimbursement policies for ATMP, compared to existing alternative treatments for the pathology. WP4 applies these methods in a series of case studies. WP5 validates the framework and WP6 coordinates the project and disseminates results.

Expected impact:

Promotion of talent and employability: Develop expertise of existing researchers in health economics, and train a new generation.

Strengthen and develop leadership in the generation of scientific knowledge: Consolidate groups working on health economics across Spain and enhance the role of the regional agency (AND&TATA) in supporting the translation of basic science into effective innovation.

Accelerate private investment in R&D&I and the competitiveness of innovative enterprises: Provide public agencies with methodological and empirical tools to encourage biotech companies to invest wisely in these therapies in Andalucía and Spain, and allocate scarce research capital more effectively.

Research orientated to the challenges of society: The project will provide information and workable recommendations for decision makers on how to evaluate ATMP and set prices and reimbursement policies. These recommendations will be orientated towards providing patients with effective, safe and affordable healthcare, while taking account of the multiple criteria demanded by patients and society at large.

Open R&D&I: Results will be diffused widely in scientific conferences and journals, and in a form accessible to different stakeholder groups and the general public. Permissions will be obtained to use patient data for the planned case studies from data owners and ethical committees, if necessary.

Synergy and policies of R&D&I at regional, national and European levels: Working links will be actively sought with existing ongoing scientific projects in ATMP at national and European level.

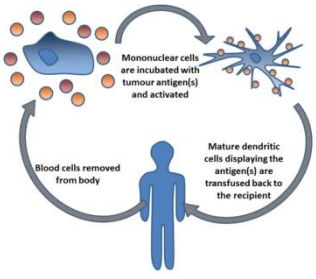
1. PROPUESTA CIENTÍFICA - *SCIENTIFIC PROPOSAL*

1.1 Background

Introduction

Access to high quality and comprehensive health care is an essential pillar of the modern welfare state. While countries differ widely in the way healthcare is financed and provided, most European countries have established universal healthcare systems that are free or heavily subsidised at the point of use. As well as providing health and financial security for citizens, the health care service and its satellite public and private industries are substantial generators of economic wealth in their own right, providing employment to millions of people, and respond to the diverse needs of patients by undertaking research, innovation and investment in new products and techniques, often at the cutting-edge of science and technology.

Hence the efficient employment of society's resources in healthcare is a matter of primary importance. Apart from brief downturns related to the economic cycle, expenditure on healthcare has grown at a fast pace over the past decades, and now represents around 9% of GDP on average across OECD countries (https://data.oecd.org/healthres/health-spending.htm). There are many factors – demographic, medical, social etc. - involved in this growth, but one concern is that the prices of new therapies are extremely high (Moreno and Epstein 2019). Many countries, including Spain, have now put in place legal-administrative procedures to decide on a case-by-case basis whether a particular new medicine or other healthcare product should be financed in the public system(Lopez-Bastida et al.2010). At present, broad criteria for decisions on medicines are set by the Ley de Garantias, and include a) severity of the disease; b) the specific needs of certain groups of people; c) the therapeutic and social value of the medicine and incremental clinical benefit taking into account its cost-effectiveness; d) the rational use of public expenditure and the budget impact to the health service; e) the existence of therapeutic alternatives at lower price; and f) the degree of innovation of the medicine. As yet, none of these indicators have been operationalized at national level (Epstein & Espin 2019, Oliva et al, forthcoming). While Spain has a well-established agency for the assessment of the efficacy of new medicines (Agencia Española de Medicamentos y Productos Sanitarios, AEMPS), and a articulated network of regional agencies (RedETS) that evaluate the effectiveness and cost-effectiveness of non-medicinal products (diagnostic tools, screening programs etc.), there is no independent national evaluation agency that is responsible for establishing the economic value of new medicines, and Spain lacks transparent procedures and objective criteria for negotiating prices with manufacturers or deciding whether those medicines should be financed by the National Health Service (NHS) (Oliva et al 2019). Steps have recently been taken towards improving this situation with the establishment in March 2019 of the National Advisory Committee (Comité Asesor para la Financiación Farmaceútica del Sistema Nacional de Salud) http://economia.uc3m.es/2019/04/09/felix-lobo-nuevo-presidente-del-comite-asesor-para-la-financiacion-farmaceutica-del-sistema-nacional-de-salud/. The project will contribute in this respect to advance the evaluation of medicines in Spain, and will make links to share knowledge and evidence with health technology assessment (HTA) agencies elsewhere, in particular NICE in the UK, and the European HTA collaboration network (EUnetHTA, www.eunethta.eu).



The overall aim of this project is to undertake theoretical work and empirical studies related to the economic evaluation of a particular class of health technologies known as Advanced Therapy Medicinal Products (ATMP). These are medicines for human use that are based on genes, tissues or cells. They are novel biotherapeutic products for treatment of chronic, degenerative and/or life-

threatening diseases, and can be classified into three types: cell therapy, gene therapy and tissue engineering. There are several ongoing initiatives at European level aimed at consolidating research effort to make Europe a world-leader in these area (e.g. RESTORE Health by Advanced Therapies https://cordis.europa.eu/project/rcn/223715/factsheet/en). The Andalusian Network for Design And Translation of Advanced Therapies (AND&TATA) coordinates the development of such therapies in Andalucía, and individual hospitals elsewhere in Spain are also active in development of ATMP (for example, Hospital La Fé, Valencia and Fundación Jiménez Díaz, Madrid). It is estimated that there are over 600 gene and cellular therapies currently in development, and by 2030 about 350.000 patients will have been treated with 30 to 60 products (Quinn et al 2019). However, for a number of reasons, such therapies often fail to translate into commercial success(Ponce et al 2018). Several ATMP have initially received marketing approval by the European Medicines Agency (EMA) only to have it withdrawn at a later review. The failure of an ATMP to break through into commercial success represents a waste of scarce research capital and resources, which could have been more productively employed elsewhere (Sharma et al. 2018). Furthermore, it may represent a potential loss to patients, if they are denied access to (potentially) promising new treatments. There is therefore an urgent need to establish new assessment and evaluation models to improve the innovation strategy and measure the real value and opportunity cost of these types of investments.

In general terms, the purpose of an evaluative framework for any healthcare therapy or program is threefold. First, it provides a set of objective criteria for deciding whether a particular product should be financed in the public NHS or not, that is, whether it offers sufficient value-for-money in comparison with other therapies and health programs. The critical issue here is that resources in the health care system are limited. Hence adding an expensive new therapy or program to the NHS will mean that some other therapy (perhaps in an entirely different area) cannot be afforded, and hence decision-makers must be sure that the new therapy offers greater benefits to the health of the population as a whole than the therapy or therapies that are displaced. Secondly, for new innovations, the evaluative framework can provide a guide to help payers design or negotiate a pricing and reimbursement scheme that is both affordable for health care payers and offers manufacturers reasonable incentives to invest in R&D. This reimbursement scheme might encompass the maximum price at which therapy could be sold (the “value-based” price) and also whether the payments to manufacturers depend on certain conditions being met (e.g “payment by results” or risk-sharing agreements). Third, an evaluative framework can offer a system and set of criteria for manufacturers and other stakeholders to sequentially decide whether to continue investment in research or development (or not) at distinct points in the life-cycle of a potential new innovation (“go / no-go” decisions).

The evaluation of the real value and opportunity cost of ATMP technologies may need to take account of a wider range of outcomes and issues than provided by traditional models of pharmaco-economics. The traditional model of evaluation typically measures the effectiveness of a therapy in terms of quality-adjusted life years (QALY) and the costs of the therapy in terms of the resources employed, according to a standard methodology(Lopez-Bastida et al 2010). The incremental cost-effectiveness ratio (ICER) is then calculated as the difference in costs (compared to the best alternative care) divided by the difference in QALY. This ratio can be compared with the usual willingness to pay for a QALY, as expressed by the body responsible for deciding pricing and reimbursement of new healthcare products. For example, in the UK, the decision-making body (the National Institute for Health and Care Excellence) have stated that the National Health Service should be willing to pay up to £20,000-30,000 per additional QALY (sometimes more for special cases). The equivalent national body for deciding price and reimbursement of medicines in Spain has not stated any explicit threshold, although empirical work has established that it could be around 22,000-25.000€ / QALY (Vallejo-Torres et al 2018).

This evaluative framework, known as “cost-effectiveness analysis” (CEA), has proved a robust and adaptable means of establishing whether a particular therapy offers value for money, compared with all the other feasible alternatives for that type of patient. ATMP contain a number of special features and challenges that need to be considered. One of the

major themes is to how to align evidence-gathering, assessment and reimbursement procedures so that promising innovation is advanced, decision-makers obtain the evidence they need about effectiveness and safety, and patients can access effective therapies at prices that are affordable for health care systems.

Firstly, the evaluation of ATMP takes place in a different legal, ethical and regulatory framework than conventional medicines. This legal-regulatory framework is designed to protect against specific environmental and health risks arising from the use of genetically modified organisms and biological products, such as the risk of transmission of animal apongiform encephalopathy agents, and specific ethical issues around the use of human cells and organs in development, testing and manufacture. Under EMA regulations, member states can permit the use of ATMP in their territories without the need for EMA marketing authorisation (either for “compassionate use” or “hospital exemption”). Hospital exception applies only to custom-made ATMPs used in a hospital setting for a specific patient. The obvious advantage of the exemption is that patients can receive much needed ATMP treatments when no products have been authorised and continue to benefit from ongoing clinical research, particularly in areas of unmet medical need. Hospital exemption ATMPs can also be a valuable source of clinical experience supporting future marketing authorisation applications. However, a challenge in Spain and elsewhere is that evaluation procedures to obtain the exemption are slow, and products developed under exemption may not build up the necessary evidence base for marketing approval. Only one hospital exception has been granted so far in Spain. Furthermore, since individual member states and indeed individual hospitals can be working on similar therapies, this exemption can lead to lack of transparency and fragmentation of research effort (https://www.ema.europa.eu/en/human-regulatory/overview/advanced-therapy-medicinal-products-overview).

Secondly, ATMP are often targeted at rare diseases. This complicates and increases the cost of clinical testing, as there are few cases, and the manufacturer needs to recover the high initial investment and clinical testing cost across a small number of patients. Furthermore, the biological nature of the therapy makes it difficult to obtain economies of scale in the complex manufacturing processes. These factors combine together to make the prices of such therapies very expensive and/or logistically complex to administer to patients. On the other hand, the small number of patients in the clinical trials means that there is sometimes considerable uncertainty about the “true” clinical benefits. EMA regulators and counterparts in other jurisdictions are now fast-tracking certain therapies for early approval with less complete clinical data than normally required. This can also lead to few patients enrolled in clinical studies, and/or without a control group (single-arm studies). Observational data can be used to compare outcomes between alternative therapies though such methods need to be used with caution to minimise the risk of bias. This poses a difficult challenge for payers and healthcare systems, who face the prospect of paying extremely high prices for therapies with uncertain clinical results. Academics, payers and regulators have proposed a number of possible solutions to this challenge, including adaptive licensing, conditional reimbursement and risk-sharing agreements (Espín, Rovira & Garcia Mochon 2011). What these schemes have in common is the need for continuing data collection post-authorisation in order to establish the effectiveness of the therapy in clinical practice (“real-world data”) (Rothery, et al 2017).

Third, developers of ATMPs, who are often small enterprises or spin-offs (incubators) from academia, require support to navigate the regulatory framework and would benefit from further access to capital investment and incentives. Andalucía has an extensive network of laboratories and health providers active in research, and AND&TATA has the mission to help translate these initiatives into commercial and clinical success to generate benefits for patients and wealth in the region, including actively seeking business collaboration. The potential of ATMP to generate positive spillover effects for multiple stakeholders may require a societal perspective in the assessment of the benefits and costs of these investments (Husereau et al 2019).

Fourth, ATMPs offer potentially “curative” therapies, often with a “one-off” treatment (Barlow et al, 2019, Faulkner et al 2019, Pearson et al. 2019). The prospect of a complete cure offers tremendous opportunities for patients, but, paradoxically, it can also be a challenge to find a suitable pricing and reimbursement (P&R) model that is both affordable for payers and gives manufacturers a return on investment in ATMP that properly compensates for the business risk. The usual approach recommended in the literature is value-based pricing, in which the price of a new therapy is set in proportion to its expected added therapeutic value(Moreno & Epstein 2019). Nevertheless, for curative treatments, it may not only be the “overall price” that is important, but also the timing of payments and with what conditions (Yeung et al 2019). Investors may prefer to invest their capital in products that require “repeat treatments” if these are perceived as being preferable over the long run than one-off payments. Likewise, if initial prices are high, and outcomes are uncertain, payers may prefer to “amortise” payments over several years (akin to a lease arrangement) rather than incur a large “one-off” payment. A number of potential P&R models have been proposed, and some assessment of the practical viability of these is required (Towse & Fenwick 2019).

These considerations indicate that there is an urgent need to establish suitable assessment models to improve the innovation strategy and measure the real value and opportunity cost of investment in these therapies (Ponce et al 2018). Up to now, a total of 22 ATMPs have been submitted to the European Medicines Agency (EMA) of which 13 were approved (Bravery 2019). However, the first four ATMPs to be approved (Chondrocelect, Glybera, MACI and Provenge), between 2009 and 2013, were finally withdrawn, mostly due to pricing and reimbursement issues (Abou-El-Enein, Elsanhoury and Reinke, 2016; Yu *et al.*, 2018). In this regard, the withdrawal of these ATMPs, with the exception of Glybera, doesn't come from safety issues or poor benefit-risk assessment (de Wilde *et al.*, 2018), but from unrealistic business models, which led to subsequent unsuccessful patient access. Kymriah and Yescarta are examples of breakthroughs for cancer patients, but also underline that these treatments come at very high prices, and many uncertainties remain about their risks and benefits (Marsden & Towse 2017). Moreover, a much greater number of ATMPs never reach regulatory approval stage. The recent EMA approval of Kymriah and Yescarta has stimulated significant interest in pursuing these issues (for example in Spain, Proyecto RET-A in cancer therapies http://weber.org.es/weber-pone-en-marcha-el-proyecto-ret-a-reflexion-estrategica-sobre-el-manejo-e-implementacion-de-las-nuevas-terapias-avanzadas/) and this is likely to be an area where investing in developing knowledge and skills in health economics will pay off in terms of major national and international repercussion. This is new work and has not received funding from any other source.

Working hypothesis

The working hypothesis is that consensual and practical recommendations can be made to (i) guide efficient investment decisions, (ii) establish objective criteria for approval, and (iii) design pricing and reimbursement schemes that allow patients to access effective ATMP at affordable prices for health systems.

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1.2. General objectives

The project will work towards recommending practical criteria for establishing the value and opportunity cost of innovative advanced therapy medicinal products, so that patients can access effective innovative therapies at prices that are affordable for health care systems. Spain has a number of exciting scientific initiatives in this field but, so far, there has been little attention given to setting out a framework for measuring the social return associated with these investments.

Given these considerations, it is necessary to:

- Establish working guidelines for investment decisions (go/no go) by private and public investors in these therapies at distinct points in the life cycle
- Recommend clear, consensual and practical criteria that decision makers in the national health service can use for establishing the price of such therapies and whether they should be financed in the NHS, and instruments (such as cost-effectiveness and the grade of innovation) for measuring whether those criteria have been met.
- Consider the merits of distinct options for how such therapies might be reimbursed, for example, through risk-sharing schemes

Research challenge 6: Social sciences, Humanities and Science with and for Society, aimed at supporting Health, Demographic Change and Well-being

1.3. Specific objectives

The specific objectives and associated work packages and tasks are

1) Review of the factors associated with success and failure of ATMP
2) Focused interviews with representatives of stakeholder groups (patients, health policy makers, health professionals, manufacturers) about their priorities and evaluative criteria
3) Development of a theoretical framework for assessing social and economic value of ATMP that encompasses
    a. Cost-effectiveness compared with all relevant alternative therapies
    b. Social impact
    c. Degree of innovation
    d. Guidelines for go/ no-go decisions over the innovation life-cycle
    e. Pricing and reimbursement options
4) Conduct empirical case studies
    a. Selection of 3 pertinent case studies
    b. Evidence collection from literature and patient
    c. Application of the theoretical frameworks developed in objective (3)
5) Validation of framework among stakeholder groups
6) Publication and dissemination

1.4. Work plan, methodology and research group

Summary of research group (equipo de investigación) and work group (equipo de trabajo)

The project is a collaboration at institutional level between the Department of Applied Economics, University of Granada (UGR), the Escuela Andaluza de Salud Publica (EASP), the Andalucian Health Technology Agency (AETSA) and Andalusian Network for Design And Translation of Advanced Therapies (AND&TATA).

The Faculty of Economics and Business Studies in the UGR is one of the largest in Spain with over 400 teaching staff and 6.000 students. Members of the project team at the Department of Applied Economics participate in several European H2020 and national research projects. The Department includes several prestigous researchers in health economics, who will be able to provide general guidance and feedback, among them Dolores Jimenez Rubio, Juan de Dios Jimenez Aguilera, Jose Martin Martin, Maria del Puerto Gonzalez, and Roberto Montero.

The Andalusian Network for Design And Traslation of Advanced Therapies (AND&TATA) has played a relevant role in the development of the field of ATMPs in Andalusia with the sponsorship of 27 clinical trials, testing both cell therapies and tissue engineering products. These clinical trials, ranging from phase I/II to phase IIb, comprise a variety of medical areas such as peripheral vascular diseases, cardiology, neurology, hematology, digestive system, ophthalmology, infectious diseases, oncology and dermatology. AND&TATA has promoted

the development of an innovative artificial skin based on tissue engineering within the Public Healthcare System, highlighting the pioneering role of this institution(https://www.juntadeandalucia.es/terapiasavanzadas). Not only is AND&TATA sponsor of these clinical trials, but they also investigate other regulatory pathways to facilitate the patient access to these innovative products. Accordingly, AND&TATA counts in their pipeline with some ATMPs that have been administered to patients through compassionate use and they are currently pending AEMPS' response regarding the approval to administer some of these ATMPs through hospital exemption. AND&TAT has set up a series of strategic alliances. Some of their sponsored clinical trials carried out in collaboration with other Regional Communities. At national level, AND&TAT is a member of the Medical Technology Innovation Platform (ITEMAS), and at international level, the Alliance for Regenerative Medicine and the International Society for Cellular Therapy.

AETSA plays a pivotal role in the healthcare system of Andalusia, but their influence reaches further beyond. At a national level, AETSA is a member of the Red Española de Agencias de Evaluación de Tecnologías Sanitarias y Prestaciones del Sistema Nacional de Salud (REDETS). AETSA collaborates with neighbouring European agencies through EUnetHTA, (see for example https://www.eunethta.eu/ja3-archive/work-package-5-life-cycle-approach-to-improve-evidence-generation/), and at an international level they are members of the International Network of Agencies for Health Technology Assessment (INAHTA).

Fundación Progreso y Salud
CONSEJERÍA DE SALUD Y FAMILIAS

The EASP is a strategic and instrumental company of the regional and national health service for the innovation of health systems, the improvement of population's health, and the promotion of scientific and technical collaboration and exchange, at national and international level.

Escuela Andaluza de Salud Pública
CONSEJERÍA DE SALUD Y FAMILIAS

Research group (n=7)

David Epstein (DE). PhD. Associate Professor, UGR. Tasks: Principal Investigator and coordinator of the work packages. Person-months in project: 7

Jaime Espín (JE). PhD. Professor, EASP. Specialist in pharmaceutical pricing and reimbursement policy. Task Leader: P&R (3.5 and 4.7). Person-months in project: 3

Antonio Olry de Labry Lima (AOL). PhD. Qualified pharmacist and health sciences researcher, EASP. Leader for CEA, societal impact and SROI (WP 3 and 4). Person-months in project: 3

Roke Iñaki Oruezabal Guijarro (RIOG). Masters. Head of Innovation & Development, AND&TATA. Leader for consultation with experts (Task 1.2), stakeholder analysis (WP2), case studies (4.1 and 4.2), validation (WP5). Person-months in project: 3

Juan Carlos Rejon Parilla (JCR). Masters. Qualified pharmacist and Senior Economist, AETSA. Expert in health policy. Leader for innovation (3.3 & 4.5). Person-months in project:3

Rosario Mata Alcazar-Caballero (RM). Doctor in Medicine. Clinical scientist, AND&TATA. Leader for stakeholder analysis (WP2), case studies (4.1) and ethics (6.2). Person-months in project: 3

Juan Antonio Blasco (JAB). Doctor in Preventative Medicine & Public Health. Scientific coordinator, AETSA. Task leader: Literature review (1.1), and implementation (4.8). Person-months in project: 3

Work group (n=9)

Marta Trapero-Bertran (MTB).PhD. Professor of Economics at UIC, Barcelona. Expert in health economics and health policy. Task: Member of expert advisory group. Person-months in project: 0.5

Richard Grieve (RG). PhD. Professor of Health Economic Methodology, London School of Hygiene and Tropical Medicine. Task: Member of expert advisory group. Person-months in project: 0.5

Marta Ortega-Ortega (MOO). PhD. Associate Professor at University of Complutense, Madrid. Expert on health economic costs and impact of diseases on productivity. Task: Support for impact of therapies on work productivity and social costs. Person-months in project: 1.5

Leticia Garcia-Mochon (LGM). PhD. Researcher, EASP. Expert on quantitative methods and decision modelling in health service research. Task: Support for SROI and CEA. Person-months in project: 3

Fabiola Lora Ulgar (FL). Masters. Coordinator of clinical operations and pharmacovigilance, AND&TATA. Task: support for evidence collection for case studies. Person-months in project: 3

Daniel Perez Troncoso (DP). Masters. Phd Student and investigator, UGR. Task: support for methodological development, evidence collection and modelling work and website design, management. Person-months in project: 6

Modou Diop Wayal (MD). Masters. Phd Student and investigator, UGR. Task: support for methodological development, evidence collection and modelling work. Person-months in project: 6

Lorena Aguilera (LA). Masters. Biotechnology scientist, AETSA. Task: Support for literature review. Person-months in project: 6

Angela Ponce (AP). Masters. Technological Translation & Development Technician, AND&TATA. Task: Support for social return on investment. Person-months in project: 6

Work plan and methodology

Work package 1. Review of the factors associated with success and failure of ATMP

The first work package will be a retrospective review of the factors associated with success and failure of previous ATMP. Building on existing the literature and in consultation with experts (policy makers, clinicians, scientists and academics), this line of work will compare for both successes and failures the clinical effectiveness of the therapy, safety issues, the benefit-risk profile, the uncertainty associated with the clinical effects, the likely resource use

impacts on the health service and other providers, the assessment procedures and criteria used by decision-makers, payment and reimbursement issues, and any special factors that may have influenced decision makers. The review aims to identify to what extent the specific challenges that prohibited technical and commercial success could have been reasonably anticipated at an earlier stage, and, if so, whether alternative policies or practices in the development process, in the pricing policy, or in the reimbursement procedures might have led to a better outcome. Around 5-6 experts will be identified from within the HTA agencies (RedETS, AEMPS) and contacts between the research team and professionals working in the field. Interviews will be conducted preferably by telephone.

Budget required: None

Task	Summary	Leader	Support	Start date	Finish date	Deliverable
1.1	Literature review	JAB	LA	1.1.20	31.3.20	Report (see WP2)
1.2	Consultation with experts	RIO	FL, JCP	1.4.20	30.6.20	

Work Package 2. Structured interviews with stakeholder groups

Given the knowledge acquired in WP1, a series of structured in-depth interviews will be carried out with selected stakeholders: patients, health policy makers / regulators, payers, health professionals, manufacturers and investors. These interviews will aim to establish stakeholder views about the prospects and challenges going forward for ensuring R&D&I in the current pipeline of ATMP leads to successful products, such as the criteria used to approve and reimburse ATMP, the role of patient participation in evidence generation and reimbursement decisions, the outcomes expected of ATMP, and the possibilities for bedside manufacturing and other techniques designed to ease logistical difficulties or reduce production costs. Social and economic barriers to access such as gender and social exclusion may be discussed if these are perceived as pertinent. The methodology for conduct of interviews and analysis of data will be based on qualitative methods (Coast 2017). Interviews will be carried out in the workplace (for professionals) or a mutually convenient location. Around 10-15 interviews are expected. With the permission of interviewee, interviews will be recorded by audio and video and edited into a short documentary-style video report that can be distributed on the project website and social media (see WP6).

Budget: Camera with in/out audio, tripod, microphone, memory cards (2), transport bag, headphones. 1500€
N-VIVO qualitative analysis software – available in Faculty
Travel costs for interviews: 300 x 15 = 4500€

Task	Summary	Leader	Support	Start date	Finish date	Deliverable
2.1	Identify & recruit stakeholders	RIO, RM	DT, MD	1.1.20	31.3.20	Report and Open Access publication on the results of WP1 and WP2.
2.2	Interviews	RIO, RM	MOO	1.4.20	31.5.20	
2.3	Qualitative analysis	RIO, RM	MD	1.6.20	31.7.20	

Work Package 3. Development of a framework for assessing social and economic value

Based on the literature review and the interviews with stakeholders, this Work Package will consist of five interconnecting tasks to develop a methodological framework for the evaluation of ATMP from the point of view of distinct stakeholders and society as a whole. This Work Package provides the methodological foundation for the associated empirical case studies (Work Package 4) and identifies the data requirements to implement each technique.

The first task is to ensure Cost Effectiveness Analysis (CEA) is appropriate to the ATMP context. CEA is required for approval of new medicines in Spain. Typically, CEA requires the systematic assessment of the therapeutic impact of the technology on patient health (compared all relevant and feasible alternative therapies) and the use of healthcare resources. Simulation or Markov modelling is used to understand the impact on health and resource use over the long term, and to evaluate the impact of plausible alternative scenarios (see for example Epstein et al. 2016, Jones, Epstein & Garcia-Mochon 2017, Epstein et al. 2018). Health is typically defined in this methodology by the quality-adjusted life year, and resource use takes account not only the cost of the therapy and adjuvant interventions but other resources that might be required to deliver the therapy (e.g. logistical support) or might be saved elsewhere in the system. In the case of (some) ATMP, the aim is to "cure" what is often a highly debilitating and disabling condition that carries an enormous burden to health and social care systems. Nevertheless, data on effectiveness and adverse events are likely to be sparse and highly uncertain. Hence considerable attention should be given to how uncertainty should be handled in CEA, typically using sensitivity analysis, scenario analysis, probabilistic models and Value of Information Analysis, and how the results of these analyses should be presented to decision-makers (Rothery 2018, Epstein 2019).

The second task is to assess whether and how CEA may need to take account of the stated aim of taking a societal perspective (Bastida-Lopez et al. 2010). This takes account not only of the impact on the health of the patient and the costs supported by the health service (payers perspective), but also non-health costs on the patient's family (formal and informal care to patients) and costs borne by wider society (productivity losses due to early mortality and morbidity) (Ortega-Ortega et al. 2015). There may also be a case for considering the "spillover effects" of successful R&D&I on wider society (Husereau et al 2019)

The third task is to consider whether the "grade of innovation" is a suitable criteria for evaluating an ATMP, and if so, to propose an objective indicator. The "Ley de Garantias" requires national health authorities to consider the grade of innovation when approving new medicines. Several quantitative indicators have been proposed in the literature (Motola et al, 2005, Motola et al. 2006, Zaragozá-García & Cuéllar 2017, Morgan 2008). However, some of these overlap with other indicators such as gravity of unmet need or comparative effectiveness. Furthermore, in all existing indicators, the scale used to rank one medicine as more "innovative" than another is arbitrary. Moreover, some authors have criticised the inclusion of an innovation criteria "per-se" in pricing and reimbursement decisions (Claxton et al 2009). Given the multidimensional nature of innovation (Mestre et al 2012), and the controversy surrounding its definition and use in P&R decisions, in this project it is proposed to use Multi Criteria Decision Analysis (MCDA), using the methodology of Espín (2018), to consensually select and weight the items that should be associated with an innovative health technology. This strand of work will be conducted among the panel of experts identified in the WP1.

The fourth task is to develop practical, operational economic guidelines for go / no-go decisions at different phases in the life-cycle of ATMP, that can be tailored to the distinct requirements of each case, and that consider the various stakeholders in the innovation process. The methodology proposed is "social return on investment"(SROI). SROI builds upon the logic of cost-benefit analysis to inform decision makers of the economic and social impact of their business, and aid governments and private donors/investors to set investment priorities so that capital and other resources can be directed at areas of maximum social impact (Cordes 2017). The information requirements and mathematical modelling techniques of SROI are similar to CEA, but conducted from the perspective of distinct stakeholders rather than wider society. When used early in the product life-cycle, when data is sparse or highly uncertain, these techniques can be used as "headroom" analysis to estimate the maximum possible selling price and, along with other indicators of the market context, provide a tool for estimating the likelihood of commercial success(Rothery et al 2018). The objective of this strand of work is to adapt the methodology to the specific challenges raised by ATMP, as described in the literature and by the interviews with stakeholders (WP1 and 2) (Ponce et al 2018).

The fifth task is to recommend pragmatic and workable regulatory, pricing and reimbursement (P&R) mechanisms that give manufacturers and payers the correct incentives, generate the necessary evidence that regulators and payers might require for regulatory approval and/or reimbursement, and allow public and private investors to recover a fair return on investment over the lifetime of the product (Rejon-Parilla et al. 2018, Rothery et al. 2018). This strand will consider strategies such as adaptive licensing, conditional approval, risk-sharing agreements and payment-by-results, and will build on knowledge gained by members of the team in previous and ongoing European research projects (MedTecHTA: http://www.medtechta.eu/ , IMPACT HTA (https://www.impact-hta.eu/) .

Budget: MCDA – 1 day meeting with 6 experts + 3 members of project team.
Travel and accommodation: 9 x 300 = 2700€

Task	Summary	Leader	Support	Start date	Finish date	Deliverables
3.1	Methods for evaluating CEA	AOL	LGM	1.9.20	31.12.20	Practical proposals for • CEA • Societal impact • Grade of innovation • SROI • P&R
3.2	Societal impact	AOL	MOO	1.9.20	31.12.20	
3.3	Degree of innovation	JCR	JE,MD	1.9.20	31.12.20	
3.4	SROI	AOL	AP	1.9.20	31.12.20	
3.5	Options for P&R	JE	JAB, JCR	1.9.20	31.12.20	Report and Open Access publication.

Work Package 4. Conduct empirical case studies

The concepts and ideas developed in the previous lines of work will be tested in a series of empirical case studies. We will aim to encompass examples of different types of ATMPs in different stages of clinical development. We will also take pathways for patient access and medical indications into consideration. The tasks in this Work Package will be:

1. Selection of 3 ATMPs suitable for case study.
2. Data-gathering (clinical evidence, resource use requirements, adverse events etc.)
3. Analysis of social return on investment and go/no-go decision
4. Cost effectiveness analysis of each therapy (compared with next best alternative)
5. Quantify the impact of each therapy compared with best alternative from a societal perspective, valuing productivity losses at work (temporary/permanent absenteeism, reduced hours and presenteeism) and the impact on family members in terms of out of pocket payments and time of caring.
6. Analysis of the degree of innovation associated with each therapy
7. Analysis of how the therapy could be priced and reimbursed in the Spanish NHS (one-off payment, risk-sharing agreement etc.)
8. Analysis of special considerations related to implementation in the Spanish NHS (e.g. learning curve effects, particular legal or ethical issues, manufacturing and logistical issues, the decentralized nature of decision making, etc.)

The final selection of case studies will be made from the clinical trials that AND&TATA has promoted. (See https://www.sspa.juntadeandalucia.es/terapiasavanzadas/images/ensayos_clinicos.pdf). These trials include diverse pathologies including stroke, major burns and eye disease, including some that have successfully completed phase 2 trials and have been licensed to a UK biotech company (Rexgenero https://rexgenero.com/). Other ATMPs already provided by the Public Healthcare System such as Kymriah (CAR-T cell therapy) could be candidates for evaluation.

Case studies will be chosen according to these criteria:

a. A set of 3 ATMP at distinct points in the development life-cycle: e.g. still under development in laboratory-based science; in phase 1 or 2 trial; know-how licensed out to a biotech company), in use under compassionate use / hospital exemption regulation; approved by EMA but awaiting approval for pricing and reimbursement.
b. The availability of data both in the intervention group and a control group comprising similar patients who receive alternative therapies. Where this is unavailable from the clinical study, we will aim to make use of existing alternative data sources (e.g. hospital patient records, other recently completed clinical trials, registries, VALTERMED, literature).
c. Ethical permission to collect and use data from patients has already been granted or can be obtained in a reasonable time period. If further new real-world data collection is considered feasible and necessary, then this will be conducted according to guidelines to ensure ethical practice, transparency, validity and credibility (https://www.npcnow.org/).

Budget: Travel and accommodation for a researcher to review hospital patient records 3 x 1000 = 3000€

Task	Summary	Leader	Support	Start date	Finish date	Deliverable
4.1	Select 3-4 ATMPs	RIO/RM	FL, AP	1.1.20	30.6.20	
4.2	Data gathering	RIO	FL, LA, AP	1.7.20	31.5.21	
4.3	CEA	AOL	LGM	1.6.21	31.3.22	
4.4	Societal impact	AOL	MOO	1.6.21	31.3.22	Report and Open Access publication on the results of the case studies.
4.5	Rating the degree of innovation	JCR	JE, MD	1.6.21	31.3.22	
4.6	SROI (go / no-go decisions)	RIO	AP	1.6.21	31.3.22	
4.7	Recommendations for P&R	JE	JCR	1.6.21	31.3.22	
4.8	Implementation	JAB	JCP, RIO	1.6.21	31.3.22	

Work Package 5. Validation of the framework among stakeholder groups

In this phase it is planned to bring together as many key stakeholders as possible in a seminar and workshop in Granada to discuss the results of the project and practical ways to implement the recommendations that emerge. The results of each of the previous phases will be presented by task leaders, and the participants will be encouraged to discuss and comment. With permissions of participants, the speakers and meeting will be recorded by audio and video and edited into a short documentary-style video report that can be distributed on the project website and social media (see WP6).

Budget: 2 day meeting 30 participants.
Research group attendees travel and accommodation: 15 [7 x 0€ (Granada) + 7 x 300€ (Sevilla, Barcelona, Madrid) + 1 x 600€ (London)] = 2700€
Stakeholder attendees travel and accommodation: 10 [10 x 500] = 5000€
Catering (working lunches) 25 x 20 x 2 = 1000€

Task	Summary	Leader	Support	Start date	Finish date	Deliverable
5.1	Internal seminar & workshop	JCR, ROI	DT,MD	1.4.22	30.6.22	Monograph with recommendations and policy implications

Work Package 6. Coordination and external diffusion

This work package handles the overall internal coordination, establish links with related projects (e.g. RESTORE Health by Advanced Therapies; RET-A: Reflexión Estratégica sobre el manejo e implementación de las nuevas Terapias Avanzadas) and relevant organisations in Spain and other countries (e.g. AEMPS, EMA, NICE), deal with ethical issues and obtain ethical committee approval, comply with financial and regulatory reporting requirements and manage external diffusion.

Budget: Web domain 300€
Travel costs (meetings, conferences etc. and publications: See 2.Expected Results Impact)

Task	Summary	Leader	Support	Start date	Finish date	Deliverable
6.1	Coordination	DE	DT	1.1.20	31.12.22	Website,
6.2	Ethics	RM	JAB	1.1.20	1.7.20	ethical approval,
6.3	Diffusion	DE	All	30.6.20	31.12.22	publications etc.

Viability of the tasks, possible risks and contingency plans

The tasks are ambitious but achievable. Members of the research group are expert in their respective areas and many have collaborated with David Epstein recently, or are in collaboration with each other. The work team includes an expert advisory group (Richard Grieve and Marta Trapero Bertran) who will provided advice and feedback on the plan, performance and outputs of the project. Marta Trapero Bertran is a member of the Comité Asesor para la Financiación Farmaceútica del Sistema Nacional de Salud and will particularly be able to advise on policy implications and implementation issues related to the recommendations made by this project. Richard Grieve is Professor of Health Economic Methodology and co-director of London School of Hygiene and Tropical Medicine centre for statistical methodology and sits on the National Institute for Health Research (UK) commissioning board.

The main area of risk is in the evidence collection for the empirical case studies. Early in the project, 3 case studies will be definitively chosen representing ATMP in distinct clinical fields and different phases of the life cycle. The specific cases will be selected where ethical permission for use of patient data is already held by AND&TATA or can reasonably be obtained within the chronology of the project.

Another area of risk is if the project is approved but the budget is less than requested. In the case that not all the costs of conferences, placements and courses can be financed then we ask for co-finance from professional societies (AES, ISPOR) and the Faculty.

Material and infrastructure
The qualitative study (WP2) will purchase inventory video recording equipment.

Chronogram (Summary, by quarter-year)

		Year1: 2020				Year2: 2021				Year3: 2022			
WP	**Topic**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
1	Literature review												
2	Interviews with stakeholders												
3	Development of frameworks												
4	Case studies												
	▪ Selection of case studies												
	▪ Evidence gathering												
	▪ Analyses												
5	Validation of framework												
6	Publication & dissemination												

Budget (summary)

Concept	Justification	Amount, €
Inventory	Recording equipment (WP2)	1,500
Travel	Interviews, meetings, conferences, seminar, placements, data collection (WP2-6)	46,310
Publication fees	Journals, monograph (WP6)	9,700
Web domain	Webpage	300
Courses	See section 3 (Training)	6,000
Audit	WP6	1,200
Total (direct cost)		65,010

2. IMPACTO ESPERADO DE LOS RESULTADOS - *EXPECTED RESULTS IMPACT*

2.1.Scientific and technical impact

The project, set within Challenge 6, undertaking research in economics and social sciences to ensure the methodology for evaluating advanced therapy medical product is appropriate and will ensure patients receive effective and safe therapies at affordable prices for the health system. These results correspond with scientific and technical objectives set out in the Plan Nacional 2017-2020 (social and economic objectives are handled in section 2.2)

- **Promotion of talent and employability (O1):** The project will develop expertise of existing researchers in technology assessment and health economics, and train a new generation. Demand is growing for professionals with this knowledge in the Public Administration, Research Institutes and Private Industry. There will be opportunities for placements of collaborators and students at partner institutions to exchange know-how.
- **Strengthen and develop leadership in the generation of scientific knowledge (O2):** The project will a) consolidate groups working on health economics across Spain b) enhance the role of AND&TATA in supporting the translation of basic science into effective innovation and ultimately successful and affordable medical therapies.

Plan for diffusion and international impact of the scientific and technical outcomes

Internal scientific meetings

The members of the research group and work group will organise a series of 3 internal scientific meetings. 6 members live in Granada, 7 in Sevilla, 1 in Madrid, 1 in Barcelona, and 1 in London.

Budget: Meeting 1, 2020, UGR Granada. 17 members [6 x 0€ + 9 x 200€ (Sevilla, Barcelona, Madrid) + 1 x 500€] plus working lunch 170€ = 2470€
Meeting 2, 2020, EASP Granada. 17 members [6 x 0€ + 9 x 200€ (Sevilla, Barcelona, Madrid) + 1 x 500€] plus working lunch 170€ = 2470€
Meeting 3, 2020, AETSA Sevilla. 17 members [7 x 0€ + 8 x 200€ (Sevilla, Barcelona, Madrid) + 1 x 500€] plus working lunch 170€ = 2270€

External seminars

It is proposed to organise a series of open external seminars for researchers and health policy experts in Spain and other European countries who are likely to be interested in the topics in this project. 3 members of the research team will be expected to attend each meeting, and each seminar is expected to reach about 10-30 expert external researchers.

Members of the project have links to Universitad Internacional Catalunya, Fundación Weber, NICE and EUNetHTA.

Budget: 1 day seminar, UIC, Barcelona (travel 3 members) 600€
1 day seminar, Fundación Weber, Madrid (travel 3 members) 600€
1 day seminar, NICE Manchester (travel & accommodation) 1500€
1 day seminar, EuNetHTA Amsterdam (travel & accommodation) 1500€

Present the results in scientific meetings, congresses and conferences

Members of the research group regularly attend the national and international conferences in their respective areas. ISPOR is well attended by academics and industry focusing on health economics. HTAi is attended by senior policy makers and staff from Health Technology Assessment agencies from around the world.

Budget: Spanish Health Economic Association congress, June 2020 and June 2021. 4 members. Travel, inscription. 750 x 4 = 3000€
HTAi June 2021. 1 member. 1500€
ISPOR November 2022. 1 member. 1500€
BioEurope 2021. 1 member. 1500€
ISCT Regional Meeting 2022. 1500€

Organise workshops of special interest groups (SIG)

It is proposed to organise a series of meetings and workshops with groups of researchers, business leaders and policy makers who have a special interest in particular topics related to this program of work, probably in Madrid. Researchers from this group are active members in ISPOR Spain Chapter and the Spanish Health Economics Association http://www.aes.es/eeconaes/presentacion/. Each meeting would be expected to attract 15-30 external attendees. A modest inscription fee will be sought from the attendees to cover the costs of the event, with no cost to the project.

Publish periodic working papers

A working paper will be made available at the completion of each Work Package, on the project website and online repository Eg.: https://econpapers.repec.org/paper/. At the completion of the project, a monograph will be published describing the methods and results of each Work Package and the overall recommendations and lessons learned.

Budget: 200€ for professional type-setting fees

Publish in national and international journals

It is expected that the project will generate 7 major papers (2 x WP1&2 + WP3 + 3 x WP4 + 1xWP5) plus the monograph described above. At an international level, the target journals for the health economics work and implementation issues will be Pharmacoeconomics and Value in Health (Q1), and Q1 clinical journals for the 3 case studies. Gaceta Sanitaria is a high quality journal Q2 that publishes health service research in Spanish and English. Target clinical/biotechnology journals include Cytotherapy, Journal of Tissue Engineering and Regenerative Medicine, Cell Stem Cell, Trends in Biotechnology y BMJ Open. Publications will be Open Access.

Budget: 1500€ each for the 6 Q1 publications
500€ for Gaceta Sanitaria. Total €9500.

Publish in blogs

Gaceta Sanitaria hosts 2 blogs related to issues in public health (an Editorial Committee one http://bloggaceta.elsevier.es/category/blog-del-comite-editorial/, and a Guest blog), and members of the group have published recently in both. AES also hosts an influential blog http://www.aes.es/blog/. No budget is required.

Disseminate results on project website, in Press Releases and Social Media

A member of the work group (DP) will build and manage the project website and monitor and manage the profile of the group in Social Media (CanalUGR, Twitter and so on). The domain fee is included in WP1

Measuring scientific and technical impact
Scientific and technical impact of the work will be measured by:

- Social media metrics (downloads, visits, retweets)
- Publications in Q1 and Q2 journals
- Citations of project in scientific newspapers and online media
- Conference presentations at national and international level
- Number of attendees at external scientific meetings and seminars

2.2. Social and economic impact

The potentially transferible results are:

- Working guidelines for investment decisions (go/no go) by private and public investors in these therapies at distinct points in the life cycle. These guidelines will be of interest to public investors (Regional Governments) and private investors (Biotechnology companies, Venture Capital funds). There are several examples of ATMP which are being developed entirely with public investment funding (e.g. artificial skin for severe burns), and there are currently no guidelines for how the public sector should evaluate these investments and ensure that scarce research capital is being wisely used. Private biotechnology industry has also drawn attention to the need for measures of value to be consistent and transparent (https://asebio.com/sites/default/files/2019-09/Plan%20INBio%20-%20Final.pdf) Results will be disseminated through the contacts that AND&TATA and AETSA have directly with these entities and more generally through press and social media.
- Clear, consensual and workable instruments for measuring 1) the cost-effectiveness of therapies for these patients 2) the social impact 3) the grade of innovation associated with ATMP. These criteria must be taken into account according to Spanish law (Ley de Garantias) but there is not yet consensus how they should be measured or the relative importance in the decision making process. These criteria and instruments will be of interest to national pharmaceutical policy-making bodies (Comisión Interministerial de Precios de Medicamentos), their advisors (Comité Asesor para la Financiación Farmaceútica del Sistema Nacional de Salud) and other evaluation agencies (Agencia Española de Medicamentos y Productos Sanitarios, RedETS). Results will be disseminated through the contacts that members of the team have with these entities, seminars and through international conferences.
- Analysis of the merits and disadvantages of distinct options for how ATMP innovations might be reimbursed, for example, through conditional approval or risk-sharing schemes, and demonstration of how these schemes can be operated in practice in concrete case studies. Currently, there is much theoretical literature about these issues, but little practical guidance on how or when distinct options should be used to solve specific problems. One of the major themes is to how to align evidence-gathering, assessment and reimbursement procedures so that patients with unmet need can access promising innovation, while at the same time decision-makers obtain the evidence they need about effectiveness and safety, at prices are affordable for health care systems.
- These reimbursement options will assist negotiations between national pharmaceutical policy-making agencies and biotechnology companies on how such innovation can be financed.

The transferible results correspond with social and economic objectives set out in the Plan Nacional 2017-2020

- **Accelerate private investment in R&D&I and the competitiveness of innovative enterprises (O3):** The project provides AND&TATA with methodological and empirical tools to encourage biotech companies to invest in these therapies in Andalucia and Spain, and allocate scarce research capital more effectively.
- **Research orientated to the challenges of society (O4)**:The project will provide information and workable recommendations for decision makers on how to evaluate ATMP and set prices and reimbursement policies. These recommendations will be orientated towards providing patients with effective, safe and affordable healthcare, while taking account of the multiple criteria demanded by patients and society at large.
- **Open R&D&I (O5)**: Results will be diffused widely in scientific conferences and Open Access journals, and in a form accessible to different stakeholder groups and the general public. Permissions will be obtained to use patient data for the planned case studies from data owners and ethical committees, if necessary.
- **Synergy and policies of R&D&I at regional, national and European levels (O6)**: Working links will be made with existing ongoing projects with complementary objectives (RET-A working on cancer immunotherapies, RESTORE at European level, VALTERMED (Information System to determine the therapeutic value in real clinical practice of medicines with high health and economic impact)

Measuring social and economic impact

Social and economic impact of the work will be measured by:

- Employment of the PhD students linked to the project after training
- Recognition and discussion of results and recommendations of the Project in national policy-making forums **(**e.g. Comité Asesor para la Financiación Farmaceútica del Sistema Nacional de Salud; and Agencia Española de Medicamentos y Productos Sanitarios)
- Recognition and citation of results and recommendations by health-professional societies (Sociedad Española de Salud Pública, Sociedad Española de Farmacia Hospitalaria)
- Citation of the project in medical- industry newspapers (El Global, Redacción Médica, Diario Medico)

3. CAPACIDAD FORMATIVA - *TRAINING CAPACITY*

3.1 Doctoral program, courses for specialization and brief placements in other centres

The project does not request any further training contracts, as the group has sufficient capacity to cover the work. However, four members of the group are in a PhD program or are initiating their doctoral studies in 2019, while others are young researchers who will benefit from training opportunities and hands-on experience of working closely with senior colleagues. Hence the arrangements for pre-doctoral and professional training are described in this section. 2 members of the work team (DP and MOO) will benefit from specialist training courses in economic evaluation (Decision Analytic Modelling for Economic Evaluation, Foundation and Advanced Modules) at the University of York, UK. Two placements are planned; the first for one of the PhD students at Granada to work 4 months at AND&TATA to set up data collection and the second for another of the PhD students to work 4 months at an international HTA agency or research institution (such as NICE, Manchester UK or EUNetHTA) to build synergies and write up papers. Members of the research team have close links with both. There may also be opportunities to be involved in related projects at European (IMPACT-HTA, STARS, EUnetHTA JA3 Work Package 5) and national level in which members of the research team are collaborators.

Budget: 4 months at AND&TATA, Sevilla (accommodation, travel and subsistence) 3,000€
4 months at international HTA agency (accommodation, travel and subsistence) 4,000€
Course fee 2200 x 2 = 4,400€
Travel and accommodation 4 days 800 x 2 = 1,600€

3.2 Relation with other doctoral theses or underway (members of project team highlighted)

PhD studies underway
Zuzana Spacirova, Economic evaluation of public health technologies, Start: 19.10.2015 (expected end Dec. 2019). Tutor: **David Epstein**. Publications: Špacírová Z**, Epstein D, García-Mochón L**, et al. Cost-effectiveness of a primary care-based exercise intervention in perimenopausal women. The FLAMENCO Project. Gaceta Sanitaria (online): https://doi.org/10.1016/j.gaceta.2018.05.012
Modou Diop, Estimation of the value of health and healthcare, Start: 26.11.2018. Tutor: **David Epstein**
Samuel López López, Financial catastrophism and sociodemographic factors associated with health payments in Spain. Start: 10.10.2018. Tutor: **Marta Ortega**
Daniel Perez Troncoso, (in application). Tutor: **David Epstein**
Juan Carlos Rejon Parilla, (in application). Tutor: **David Epstein & Jaime Espín**. Publications: see reference list in this proposal
Lorena Aguilera, Biotechnology (University of Malaga), Start: 01.11.2018. Tutor: Gonzalo Claros
PhD completed
Eva Martin Ruiz, La prevención primaria de eventos cardiovasculares. Defended: 28.9.2018 Cum laude. Tutors: **Antonio Olry** & Ricardo Osuña. Publications: E Martín-Ruiz, **A Olry-de-Labry-Lima, D Epstein**, 2018 Primary prevention of cardiovascular disease: an umbrella review of non-pharmacological interventions Prevención primaria de enfermedades cardiovasculares. Anales de Navarra. 41 (3), 355-369 E Martin-Ruiz, **A Olry-de-Labry-Lima**, R Ocana-Riola, **D Epstein** 2018. Systematic review of the effect of adherence to statin treatment on critical cardiovascular events and mortality in primary prevention. Journal of cardiovascular pharmacology and therapeutics 23 (3), 200-215
Masters students with publications and/or prizes
Rafael Ruiz Montero, Evaluación económica de la inclusión en el calendario vacunal de 4CMenB. 31.7.2019. Accésit 16ª Edición de los Premios Profesor Barea. Tutors: **Jaime Espín & David Epstein.** Publications: Accepted in Gaceta Sanitaria

4. CONDICIONES ESPECÍFICAS PARA LA EJECUCIÓN DE DETERMINADOS PROYECTOS - *SPECIFIC CONDITIONS FOR THE EXECUTION OF CERTAIN PROJECTS*

Ethical committee approval from the UGR will be sought to use patient data collected within existing clinical studies. AND&TATA is the promoter of these clinical studies and already has ethical approval and patient consent to participate in research projects. Relevant data from these studies will be stored on a password-secured server in a locked room at UGR