# THE ECONOMIC EVALUATION OF ADVANCED THERAPY MEDICINAL PRODUCTS: CHARACTERISTICS AND REASONS FOR A NEW ECONOMIC AND ACCOUNTING APPROACH

## Technical Policy Report from the #VITA[1] Working Group[2]

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[1] **#VITA** (Valore ed Innovazione delle Terapie Avanzate) is a group of pharmaceutical companies specialised in the advanced therapy medicinal products (ATMPs) sector that, with the involvement of various reference stakeholders, aim to promote an interest group for the Value and Innovation of Advanced Therapies (**#VITA**) with the following objectives:

(a) disseminating knowledge transparently among the various stakeholders about the innovative value and therapeutic benefits of ATMPs for patients and citizens;

(b) ensuring that those stakeholders acquire objective facts and data about the opportunities and critical aspects associated with ATMPs so as to initiate a constructive dialogue to guarantee that patients and healthcare institutions have prompt access to innovation.

[2] #VITA Working Group, coordinated by Avv. Rosanna Sovani (Partner of LS CUBE Studio Legale), is composed by Prof. Mauro Marè (Professor of Finance Science University of Tuscia and LUISS Guido Carli), Prof. Americo Cicchetti (Catholic University and Director of ALTEMS) and Avv. Paola La Licata (Partner of LS CUBE Studio Legale).

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## Executive Summary

The development of advanced therapies *(ATMP: Advanced Therapy Medicinal Products)* presents new opportunities for the treatment and prevention of a variety of diseases (gene diseases, oncological diseases and diseases with long prognosis) or for restoring, correcting or modifying compromised physiological functions in humans, including by correcting mutations acquired on a genetic basis.

The relevance of these innovative therapies, however, places them at the centre of the discussion on health and health policy choices for the future and the sustainability of the health service. This will pose very delicate problems of choice and rationing in terms of access to treatment for patients, which could result in the treatment of fewer patients than eligible and therefore potentially treatable.

A solution in terms of identifying the resources with which to finance them must therefore be tackled today so as not to arrive unprepared.

ATMPs are different from traditional medicines and are characterised by:

- being one-shot, that is, they are administered with a single treatment, unlike the traditional drugs and protocols used for other pathologies, which provide repeated and regular treatment, with a clear time misalignment between current costs, concentrated in the short term, and future benefits, spread over a longer time horizon;
- high investment costs, but also significant benefits in clinical, therapeutic, social and economic terms for health systems and patient health;
- offering new prospects for recovery to patients suffering from pathologies that, until now, lacked a therapeutic solution;
- taking direct action on the causes of the disease;
- requiring a long and more complex preparation process than traditional medicines;
- being biological medicinal products composed of the same cells as the patients, which are taken from the hospital and then engineered in the company's production sites;
- being administered only in qualified and specialized centers and are born from extremely innovative and complex platforms;
- requiring continuous maintenance and innovation during their life cycle management to be updated and to ensure the best possible product for patients;
- generating additional benefits in terms of recovering productivity at work over long periods of life which is improved in its psychological, relational and social aspects;
- generating impacts on other levels of care in the healthcare system as they involve hospital resources in the care process;
- involving co-responsibility for treatment outcomes between the pharmaceutical industry and the health care system that intervenes with expertise and other technologies to support the treatment process.

Considering the intrinsic characteristics of ATMPs and the emerging knowledge and awareness on the part of patients that is causing a growing demand, facing the NHS with difficult economic and moral choices, the Technical Policy Report proposes a new method of financing (fractionated and instalment beyond the financial year and outcome based). This model provides for a mechanism of risk sharing between the NHS and the companies producing the possible clinical results: if at any time during the instalment period the treatment is not effective, the NHS will not have to pay the subsequent annual instalments, which will thus be borne by the companies producing the treatment.

With this method of installment, **the NHS would be in a position to compensate the annual expenditure with the savings for the NHS generated by the therapy in the same current year and guarantee access to treatment to a large number of potentially eligible patients**.

The percentage of expenditure payable in instalments for the purchase of advanced therapies by the NHS, **having obvious elements of an expenditure with benefits deferred over time, can be considered a substantially investment expenditure and therefore be as such accounted for**. On the other hand, the need to consider the investment component of some public expenditures is clear and has already emerged some time ago in the discussions on public accounting and in the system of national accounts harmonised between countries adopted by the UN and the European Union.

Hence the possibility of **building an ad hoc rule with a specific authorisation of expenditure of a multiannual nature with aligned legal competence and economic competence, including in terms of financial coverage. This is in fact already possible with the existing accounting standards** as amended by the implementing decrees of the accounting and public finance reform of Law 196/2009 (including Legislative Decree 116/2018 and Legislative Decree 29/2018).

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## 1. The challenge of ATMPs

In recent decades, developments in molecular and cell biology and the progress achieved in DNA analysis have radically transformed the biomedical field in terms of providing treatment for various genome-based pathologies. In particular, new gene- and cell-based therapies have become established in recent years (so-called advanced therapies), which have enormous promise in the treatment, and in some cases even the resolution, of pathologies that had been considered untreatable until only a few years ago.

The development of advanced therapy medicinal products (ATMPs) provides new opportunities for the treatment and prevention of a range of pathologies (genetic diseases, such as cancers and diseases with lengthy prognoses) or the restoration, correction or modification of compromised physiological functions in human patients, including the correction of acquired gene-based mutations. Advanced therapies can be classified in three principal groups: gene therapies, somatic cell therapies and tissue engineering therapies.

In recent years, seven advanced therapies have been approved and marketed. 2017 was the year of Yescarta™ and Kymriah™, two CAR-T treatments introduced as advanced therapies for certain forms of haematological tumours and reimbursed by the Italian national health system, in mid-2019, both classified as innovative medicines. Luxturna™ was introduced onto the American market for a non-life-threatening condition, but is able to prevent blindness in patients suffering from rare hereditary diseases of the retina. There are also the Italian drugs Holoclar™, the first stem cell-based treatment approved and registered in 2015, for the regeneration of the cornea following severe burns, and Strimvelis™, the first *ex vivo* gene therapy product using haematopoietic stem cells intended for patients suffering from a serious genetic immunodeficiency (ADA-SCID), approved in Europe (EMA) in April 2016.

In 2019, the United States approved Zolgensma™, which is applied in a single administration to newborns or infants aged less than two years suffering from SMA1 (spinal muscular atrophy). Also in mid-2019, the European market saw the arrival of Zynteglo™ (first known as LentiGlobin) for the treatment of transfusion-dependent β-thalassaemia in adolescent and adult patients.

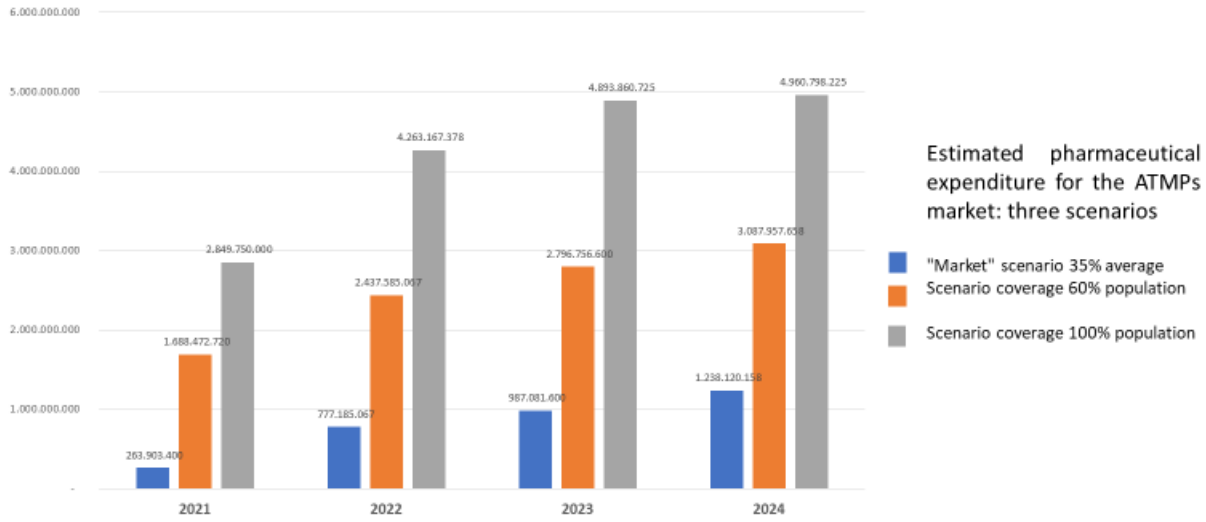
**A considerable increase in advanced therapy medicinal products is expected in the coming decade**. By 2030, up to 60 new cell and gene therapies could be launched globally, covering a total of about 350,000 and 50,000 patients each year[3].

The cost of these therapies is generally high and this clearly represents a challenge for the public purse and public health systems.

[3] Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System - Casey Quinn, PhD, Colin Young, PhD, Jonathan Thomas, BSc, Mark Trusheim, MSc, the MIT NEWDIGS FoCUS Writing Group, Center for Biomedical Innovation, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.

Find below a graph (Table 1) representing an estimate of the impact on National Health Service spending of the global ATMP market, calculated on three population scenarios: market (35% of the eligible population), 60% of the eligible population, and 100% of the eligible population.

Table 1




However, the importance of these innovative therapies puts them at the very heart of the discussion on health and public policy choices of the future. The number of patients who could potentially be treated is very high per se but could also be significant from various different standpoints (health, economic, social). This is a good news for patient expectations, in terms of quality of life and life expectancy, and it is anticipated that the next few years will see the emergence of a growing demand for these therapies through the introduction of new solutions or the extension of treatment indications already approved. This creates very sensitive issues of choice and rationing: in terms of patient access; for public health institutions, in choosing which patients to treat, which has obvious ethical implications; and lastly, and above all, for the implications for health systems and the public funding constraints in various countries, in terms of identifying resources to finance these therapies.

## 2 Characteristics of ATMPs, critical aspects and prospects

ATMPs are innovative therapies that use genetic approaches (cell- and tissue-based) for the specific purpose of repairing damaged tissues and cells. ATMPs for **gene therapy** involve the insertion of genetic material (DNA) into the cells in order to be able to treat pathologies (such as genetic diseases). This insertion procedure is known as transfection. **Compared to traditional medicines, the characteristic of these therapies is that they are much more complex to research, develop, produce and then distribute and offer to the**

**public and healthcare systems**[4]. They are characterised by a high cost profile, which reflects the costs of production (in particular, costs for research and development), delivery and management, and the commercial sustainability of these therapies.

ATMPs are highly innovative therapies and can be "curative" or "transformative"[5], which means they can modify the natural path of the pathology in a patient. In summary, the following aspects have been demonstrated:

a. these therapies have a particular health and economic profile and specific technical peculiarities. The essential characteristic in health terms is that they are **one-shot, patient-specific or for niche patient groups,** meaning they are administered in a single treatment, unlike traditional medicines and protocols used for other pathologies, which envisage repeated, regular treatments;
b. they have high investment costs but also **considerable clinical, therapeutic and economic benefits for healthcare systems and patient health**;
c. they offer **new prospects for healing patients suffering from pathologies that**, up to now, **have been lacking a therapeutic solution**;
d. unlike therapies that work to mitigate the symptoms of a condition, **advanced therapies act directly on the causes of the disease**;
e. because of their specific characteristics, **they require a lengthy and more complex preparation process compared to traditional medicines**;
f. they consist of biological medicinal products, made up of genes that produce a therapeutic, prophylactic or diagnostic effect, and involve the insertion of "recombinant" DNA into the body. **These medicines are therefore made up of the patients' own cells, which are sampled in hospital and then engineered at corporate production sites**;
g. they are **administered only in qualified, specialised centres** and result from extremely complex and innovative platforms;
h. **management of their life cycle requires continuous maintenance and innovation** to keep up-to-date and to provide patients with the best possible product.

The most technical aspects of advanced therapies in industrial and organisational terms are the following:

- the principal paradigms on which aspects such as the trialling, development, production and approval of traditional medicines have been based for years are changing;
- discovery, product engineering and innovative trial design in the preclinical and clinical phases are changing, as are manufacturing plants – in terms of management and scale-up – and final checks on the product to be put on the market;

[4] See Jorgensen-Kefalas (2017).
[5] See Chapman et al (2019).

- the procedures for access are different, as is the selection of the centres that are able to administer these therapies;
- a considerable adaptation is required to determine their pricing and funding.

One of the factors that potentially hinders the entry of advanced therapy medicinal products onto the market is the fact that these products are currently evaluated by the regulatory authorities and by HTA bodies around the world in the same way as traditional medicines. This also happens in Italy, with evaluation by the Italian Medicines Agency (AIFA). But the most important point is **that there is currently no appropriate and stable legislative and regulatory framework governing procedures for access[6], criteria for differentiated use of advanced therapies and traditional medicines, and strategies for pricing and reimbursement**[7].

In general, there is a widespread perception that these therapies are costly and the entire discussion is understandably constrained to a large extent by the cost aspect. The profile of the real and potential benefits and the direct and indirect economic advantages that these therapies can produce is completely absent from the discussion and still little analysed and inadequately evaluated.

**The volume of resources necessary to access these therapies is going to be the critical point in the future**, because this will determine whether healthcare systems are more or less prepared to support the associated cost. This situation also inevitably causes a delay in gaining access to the therapies by potential patients and a **limitation on the use of those therapies for patient subgroups within approved indications**. The evaluation of new technologies is a very complex process and **the inadequacy of traditional reimbursement and budget schemes** in covering the costs of these new protocols represents a **risk for the very availability of new therapies** for patients in Italy.

[6] Regulation (EC) No 1394/2007 currently represents the reference regulatory context for ATMPs, modifying Directive 2001/83/EC on the Community code relating to medicinal products for human use, and Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (EMA) https://www.ema.europa.eu/en. In addition, Directive 2009/120/EC (modifying Directive 2001/83/EC) has updated the definitions and detailed scientific and technical requirements for gene therapy medicinal products and somatic cell therapy medicinal products. That Directive has also established detailed scientific and technical requirements for tissue engineered products, as well as for advanced therapy medicinal products containing medical devices. The development of ATMPs must comply with Directive 2001/20/EC on the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use (Regulation (EU) No 536/2014), which lays down specific requirements for this type of medicinal product, specifically because of their complexity.

[7] Marketing authorisations for ATMPs are awarded in all cases using the centralised marketing authorisation procedure used for traditional medicinal products. The process and time-frames for the technical and scientific evaluation of the documentation submitted by the pharmaceutical company are the same as those applied for traditional medicines, although the role of the Committee for Medicinal Products for Human Use (CHMP) is supported by that of the Committee for Advanced Therapies (CAT). Furthermore, in Italy, the reimbursement process for ATMPs uses the same procedure as for traditional medicines.

It is therefore appropriate to **define a system for management and reporting** that is different for the system applied for traditional medicines, which gives due consideration to the following characteristics:

a. we are dealing with therapies created individually for individual patients;
b. there is a need for timely engineering of an individual treatment for an individual patient and no longer for the large-scale production of the same active substance;
c. these are therapies that do not involve extensive administration over time, but rather one-shot;
d. the clinical benefit for the individual patient will be evaluated along with the social costs avoided and the various types of benefit produced, both direct and indirect, which must be adequately defined and estimated;
e. because the costs are substantially concentrated within a short period and the benefits (and costs avoided) are spread over a longer time horizon, with a clear misalignment in terms of time-frame between current costs and future benefits, appropriate discount rates must be applied for future benefits in relation to the costs incurred.

## 3 The peculiarities associated with regulatory evaluation and health technology assessment (HTA) of ATMPs

In the light of the above, all regulatory agencies and Health Technology Assessment (HTA) agencies around the world recognise the need to adapt their value frameworks for technologies with such unique characteristics. There is currently a need for new value frameworks to provide appropriate support for decisions on price and reimbursement so as to guarantee, on the one hand, accessibility for patients to effective products and, on the other, fair remuneration for the risks taken and investments made by the industrial entities concerned.

Indeed, there is currently considerable debate about the possibility of applying the shared methodologies and approaches of "traditional" HTA to the context of ATMPs. Methodologies such as the Core Model®, developed by the European Network of Health Technology Assessment, do not seem to provide the level of sensitivity needed to consider such specific clinical, organisational, economic, ethical and social implications.

This fact is confirmed by a study conducted by the Canadian HTA agency (CADTH), based on a survey commenced in 2018 among the main HTA agencies and regulatory agencies globally, which has shown that there is no international alignment on the methodologies to be used for evaluation of ATMPs. The document reveals an absence of specific common guidelines or frameworks for gene therapy among HTA bodies.

In general, it is recognised that traditional HTA approaches have methodological limitations in this context. To clarify the challenges anticipated by regulatory and HTA agencies, it is

very useful to review the analysis undertaken by the Institute for Clinical and Economic Review (ICER) in Washington, which identifies four critical aspects:

- scale of uncertainty about the clinical effects, which must be observed over very long periods in order to determine actual efficacy;
- multiple dimensions to determine the "value" generated by these therapies, above all in relation to the economic, social and ethical aspects;
- misalignment in terms of time between the costs incurred to acquire the therapies and the associated clinical and social benefits, which implies a particular focus on approaches for "discounting" in cost-efficacy models;
- methods for a fair redistribution of the economic benefits among the various members of the innovation and utilisation chain, which means there is a need to develop innovative approaches for economic analysis and pricing.

The evaluation of ATMP should, therefore, take the above into account and take place in a context in which the appraisal bodies carefully analyse the impact, in terms of **benefits, on the direct and indirect costs of the therapies in question**; health expenditure and pharmaceutical expenditure should be increasingly correlated (overcoming the logic of silos). In this regard, see below a simulation carried out based on 4 ATMP data and representative of the estimated impact on the expenditure of the entire ATMP market assuming three scenarios in which the potential treatment of 35% (Table 2.), 60% (Table 3.) and 100% (Table 4.) of the eligible population is considered respectively.

*Table 2- Estimate of the impact on overall ATMP market expenditure (Market scenario = 35% of the eligible population)*

| | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|
| *Market share of 4 ATMPs* | *50% of global market** | *45% of global market** | *40% of global market** | *40% of global market** |
| **Total estimated expenditures (all market)** | **263.903.400** | **777.185.066** | **987.081.600** | **1.238.120.157** |
| Estimated SSN savings (4 ATMPs) | 11.795.305 | 142.545.951 | 150.491.345 | 210.313.207 E |
| **Estimated SSN savings (all market)** | **29.488.264** | **316.768.780** | **376.228.362** | **525.783.018** |
| Estimated SSN budget impact (4 ATMPs) | 64.655.703 | 183.227.000 | 225.738.283 | 270.771.183 |
| **Estimated SSN budget impact (all market)** | **161.639.259** | **407.171.112** | **564.345.708** | **676.927.959** |

Based on the assumption that year 1 is 2021
* The global ATMPs market estimate is based on Eder C, Wild C. 2019. Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption, *Journal of Market Access & Health Policy, Vol. 7*

*Table 3 - Estimated impact on global ATMP market expenditure (60% coverage of the eligible population)*

| | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|
| *Market share of 4 ATMPs* | *50% of global market** | *45% of global market** | *40% of global market** | *40% of global market** |
| **Total estimated expenditure (all market)** | **1.688.472.720** | **2.437.585.066** | **2.796.756.600** | **3.087.957.657** |
| Estimated SSN savings (4 ATMPs) | 11.795.305 | 142.545.951 | 150.491.345 | 210.313.207 |
| **Estimated SSN savings (all market)** | **23.590.611** | **316.768.780** | **376.228.362** | **525.783.018** |
| Estimated SSN budget impact (4 ATMPs) | 832.441.054 | 954.367.328 | 968.211.294 | 1.024.869.855 |
| **Estimated SSN budget impact (all market)** | **1.664.882.108** | **2.120.816.286** | **2.420.528.237** | **2.562.174.639** |

Based on the assumption that year 1 is 2021
* The global ATMPs market estimate is based on Eder C, Wild C. 2019. Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption, *Journal of Market Access & Health Policy, Vol. 7*

*Table 4 - Estimated impact on global ATMP market expenditure (100% coverage of the eligible population)*

| | 2021 | 2022 | 2023 | 2024 |
|---|---|---|---|---|
| *Market share of 4 ATMPs* | *50% of global market** | *45% of global market** | *40% of global market** | *40% of global market** |
| **Total estimated expenditures (all market)** | **2.849.750.000** | **4.263.167.377** | **4.893.860.725** | **4.960.798.225** |
| Estimated SSN savings (4 ATMPs) | 11.795.305 | 142.545.951 | 150.491.345 | 210.313.207 |
| **Estimated SSN savings (all market)** | **23.590.611** | **316.768.780** | **376.228.362** | **525.783.018** |
| Estimated SSN budget impact (4 ATMPs) | 1.413.079.694 | 1.775.879.368 | 1.807.052.944 | 1.774.006.082 |
| **Estimated SSN budget impact (all market)** | **2.826.159.388** | **3.946.398.597** | **4.517.632.362** | **4.435.015.206** |

Based on the assumption that year 1 is 2021
* The global ATMPs market estimate is based on Eder C, Wild C. 2019. Technology forecast: advanced therapies in late clinical research, EMA approval or clinical application via hospital exemption, *Journal of Market Access & Health Policy, Vol. 7*

In fact, pharmaceutical governance today is based on a policy of ceilings on the main spending silos, limiting any assessment to the perimeter of the Health Service, without taking into account the budgetary impacts of the State as a whole and therefore preventing a reasoning in terms of welfare in the broadest sense of the term[8]. **Overcoming the logic of**

[8] *Il servizio Sanitario Nazionale guarda al futuro. Verso nuovi e più evoluti schemi di governance- Andrea Urbani (2019)*

**the silos would, instead, allow the evaluation of a new technology that is more expensive in itself but which has an impact in terms of savings in terms of productivity, social costs, etc., not only as a cost but also in terms of investment.** The causal links between health and the economic and social system cannot be ignored, as this would prevent any assessment in terms of investment in health and health care and would be relegated to simple costs borne by the public finance system[9].

## 4 Economic evaluation of advanced therapies and reimbursement models

In terms of economic analysis, these therapies have very specific characteristics and a significant degree of asymmetry in terms of the point for between payment of costs – which are almost all upfront – and the emergence of the benefits. This is perhaps the main aspect that suggests the need for an economic and accounting evaluation of these therapies that is different and innovative.

In particular, these therapies generate **direct and indirect benefits over time**: increased life expectancy, improved quality of human life, treatment and stabilisation of various pathologies (which has a clear impact on the value of human life). But they also have benefits in terms of treatment savings and consumption of medicines and healthcare services of various kinds; reduced use of hospital services, simplifying the number and type of medical procedures and preserving the health status of patients; costs for reduction of work activities, production capacity, and even a reduced burden on families and healthcare facilities in terms of assisting patients; the possibility, following remission of the illness, of being able to continue education and participation in collective life; the positive effects for patients' work prospects; the longer horizons for potential pension liabilities; the saving in resources consumed directly by healthcare institutions and of family resources and those for direct and indirect assistance. These benefits need to be carefully evaluated and require the use of appropriate financial and economic techniques[10].

In the light of the above, the decision to establish a price for a new treatment or to determine which therapy deserves funding should be based, as far as possible, on an estimate of these overall economic effects on the healthcare system as a whole and on the health of citizens, considering not only the obvious immediate and upfront costs but also the long-term value that these generate for society[11].

In this context, the standard economic and accounting evaluation, based on an estimation of the cost of traditional drugs and therapies (which are repeated and envisage an annual treatment cycle) and on the criterion of typical budgetary economic accrual, is not at all appropriate for advanced therapies and their very specific technological and industrial characteristics. They require a new medical, economic, accounting and public finance

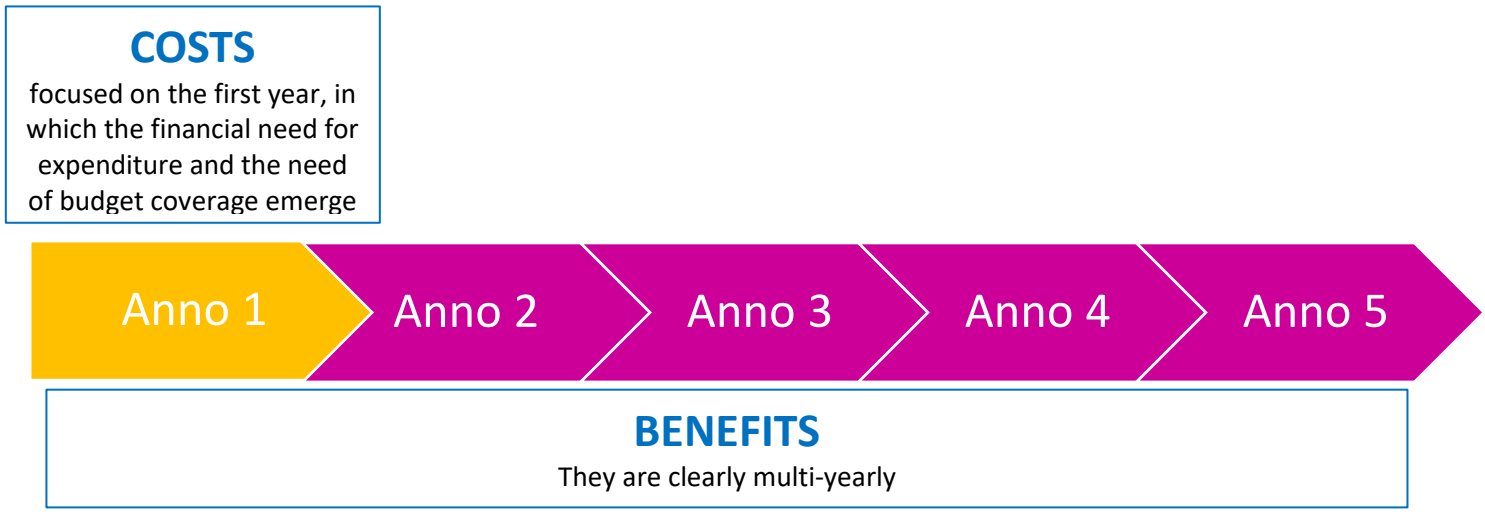
[9] *Il servizio Sanitario Nazionale guarda al futuro. Verso nuovi e più evoluti schemi di governance- Andrea Urbani (2019)*
[10] See Jorgens-Kefalas (2017), Ciarametaro at al. (2018), Duke-Margolis Center for Health Policy (2019), Salzman et al (2018), Maes at al. (2019).
[11] See ACI (2019).

approach. The efficacy of these therapies will be verified over the course of several years, when it will be possible to understand and estimate the - more or less extensive - positive effects that they have achieved in terms of protocols for treatment of the various pathologies addressed and the quality of life of patients, and thus the considerable saving in direct and indirect costs that they generate.

In relation to the economic analysis and efficacy evaluation, ATMPs therefore represent **a new challenge for public healthcare systems.** This involves understanding which therapies will be possible, given the available resources, how they should be adopted and according to which administrative, financial and accounting process – in particular, the methods and procedures for *reimbursement*, which must be appropriate for the medical substance of these therapies.

We are faced with a dilemma: these therapies condense the cost of production into a very concentrated, limited period, but have a very long-term profile for distribution of the benefits, which are not concentrated within a year but, rather, distributed over a smaller or larger number of years. This asymmetry between the distribution of costs and benefits requires an evaluation of advanced therapies using a new ad hoc approach, in economic (evaluation of costs and benefits) and accounting terms and in terms of payment flows. We need to create a management system that takes into consideration the specific characteristics of ATMPs: the different types of clinical benefit for the individual patient, the various social costs avoided, and the clear asymmetry between current costs and future benefits[12] (see Table 5.).

*Table 5.*




[12] ACI (2019) states that *"the annual costs of current treatments reflect only the price of direct medical interventions and fail to capture other costs associated with traditional treatment, including the cost of more frequent hospitalization, increased hospital readmissions, shortened longevity, reduced quality of life, paid caregiving and unpaid caregiving by family members, problems with drug adherence, lost income, reduced productivity and other labor market difficulties, as well as costs shared and covered by Medicare, health insurance providers and others"*.

The significant economic value of ATMP therapies tends to generate a considerable potential impact in the future on public sector balance sheets and those of healthcare institutions. The complex situation of Italian public finance and the existing balance sheet constraints do not allow any particular room for flexibility in this area and may even create a naturally reduced readiness within part of the public health system to support the associated costs. And yet, the medical and economic importance of these therapies, despite creating sensitive issues for budgetary constraints, means that we need to find an appropriate and economically sustainable solution for the public sector, the healthcare industry and, above all, the potential patients.

The public sector must take on this challenge and deal with this new situation, because the dissemination of the therapies in terms of supply, the growing knowledge and awareness that will emerge quickly among patients, will create specific, increasing demand for these therapies and will in any case pose difficult dilemmas for public operators in relation to complex and sensitive economic, industrial and moral decisions.

The asymmetry between costs and benefits may delay the gradual and sustainable dissemination and adoption of more effective therapies and access to those therapies for patients. At least in the very short term, within the existing legislative and regulatory context, these therapies seem destined to be limited solely to particular, very restricted patient subgroups – a circumstance that will obviously cause very delicate problems in terms of choices for public healthcare institutions and inconvenience for potential recipients: **who, and using what arguments, will explain to potential patients that access to treatments is not possible for everyone? Who will decide the thresholds for access and using what criteria?**

It should be noted that the evaluation of new technologies is a very complex process and that **the traditional reimbursement and budget schemes for coverage of the costs of these new protocols are inadequate and unsuitable** and could prejudice the availability of new therapies for patients in Italy. It therefore seems appropriate to study new systems for reimbursement and accounting of costs that are more suited to the innovative characteristics of these therapies in medical and technological terms. To guarantee patients access to this important therapeutic innovation, obviously within the limits of the available resources, we therefore need to develop new management models that go beyond the current system based on acute, recurrent pathologies.

We must therefore identify **an appropriate payment scheme**, which reduces the costs that can be borne by public health systems but avoids intense forms of rationing (or quite simply non-access) and enables rational, sustainable use of these therapies. It is also clear that comparison with other medicines is not possible, either in terms of efficacy, assessed in trials on limited patient populations, or in terms of price, because there are often no

alternative treatments, or because the potential eradication or stabilisation of a disease has value in and of itself that is not easy to determine in monetary terms.

The distribution of the benefits of gene therapies over time means that we need to look at this over a much longer period than we do for traditional medicines, in the order of several years. We then need to define a new **method of funding for ATMPs, a payment model that is staggered and can be paid in instalments based on a system of annuities**[13]. A similar payment scheme has been investigated and evaluated in several foreign trials (USA, United Kingdom, Spain, etc.[14]) and in certain academic journal articles[15].

The duration of the benefit should be estimated more precisely and should be consolidated and monitorable using a value- or outcome-based evaluation mechanism, thus making it possible to collect data on the efficacy of the therapies and define a payment programme that is appropriate and synchronised over time. Possible potential demand for these therapies should be estimated in general, not only in order to understand the cost profile that these therapies might generate over time for the public healthcare system, but also to define the possible patient groups for each therapy, and therefore the margins of choice and the optimal cost/benefit profile for each.

## 5 Structure of a new approach: which payment model for ATMPs?

Academic research[16] and payers have currently developed payment schemes such as Management Entry Agreements (MEA), agreements for conditional access to the market for innovative and/or high-cost medicines, which make it possible to provide new treatments for patients, although with a degree of uncertainty because of the lack of information about therapeutic benefits and actual costs. In particular, the principal economic and financial techniques considered are the following:

a. An agreement based on the clinical benefit expected from the new drug (outcome- or value-based scheme);
b. Payment by result: payback of 100% for all patients who do not respond to the therapy (pay-for-performance-based);
c. Annuities method: definition of an amortisation plan and a sustainable instalment profile;

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[13] "*Amortization can be considered to be similar to mortgages or loans (credit market solutions), whereby the government (or another third party) issues loans to payers to fund the upfront bill, and then the health care payer pays instalments over time, in line with realization of the benefits (Philipson and von Eschenbach, 2014). An example of this type of mechanism can be seen in Spain, where the national government announced low-interest loans for regional payers to fund high cost HCV therapies* (APMHealthEurope, 2015)." (Nice (2017).

[14] See Nice (2013, 2017, 2019), Trusheim (2019), Icer (2017), Policy Report (2019).

[15] See among various articles Slocomb-Verner (2017); Jorgens-Kefalas (2017), Maes at al. ((2019), Salzman et al (2018), Hercher-Prince (2019), Duke-Margolis Center for Health Policy (2019), Cicchetti (2019).

[16] The prospects for the various forms of payment and various costs and benefits are discussed, inter alia, in Slocomb-Verner (2017), Jorgens-Kefalas (2017), Hlavka (2018), Maes at al ((2019), Salzman et al (2018), Hercher-Prince (2019), Duke-Margolis Center for Health Policy (2019), Nice (2017, 2019), Trusheim (2019), Icer (2017), and Policy Report (2019).

d. Risk sharing (risk pools): use of a financial technique for optimal spreading of risk;
e. The definition of discounting or rebate mechanisms (usually 50% for all patients not responding to treatment) and cost sharing (definition of discounts, including up to 100%, to be applied for the initial cycles for all eligible patients;
f. Success fee: subsequent payment of 100%;
g. Financial agreements (financial-based schemes), including with third parties;
h. Capping: supply payable by the company if a certain capped value is exceeded.

MEAs are valid instruments that make it possible for the regulatory authorities to respond to the challenge of increasingly limited resources in the face of a continuous increase in the costs of new therapies. However, with the advent of new therapies**, it has become necessary to find a more appropriate payment scheme**: because these treatments are potentially curative or transformative, we need to think about them in terms of a much longer time horizon than for traditional medicines, in the order of several decades. Furthermore, comparison with other traditional medicines is not possible, either in terms of efficacy, assessed in trials on limited patient populations, or in terms of price, because there are often no alternative treatments, or because the potential eradication of a disease has value in and of itself that is not easy to monetise[17].

*5.1 The characteristics of an annuity scheme*

A payment scheme based on annuities ("Annuity Model") is based on a deferred payment model, with a mechanism for sharing of risk between the national healthcare system and the companies generating the possible clinical outcomes (verified using outcome indicators). This model would be based on the following elements:

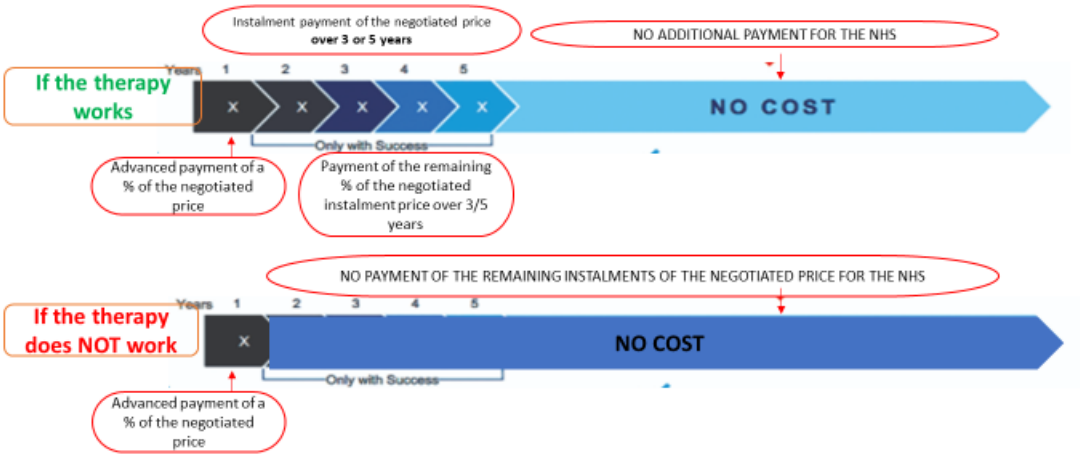
a. payment (upfront) by the national healthcare system of a percentage of the total cost of the therapy determined in advance (20%-30%), at the time when the one-shot is administered;
b. payment of the remaining percentage of the total cost in a number of annual instalments (three/five) depending on the efficacy of the therapy (instalment period)[18];
c. the national healthcare system pays for the therapy only on the basis of the outcome maintained over time. If the therapy is not effective, at any point during the instalment period, the subsequent annual instalments are not payable or may be suspended;

[17] "Gene therapies are fundamentally different. By fixing the underlying causes of genetic diseases, gene therapies offer the opportunity to fully cure disorders instead of merely alleviating their symptoms. An added advantage is that instead of needing to follow a never-ending pharmaceutical regime, patients undergoing gene therapy often only need a single dose with little follow-up care required. […] **Payers, policymakers, and manufacturers must recognize that existing mechanisms to finance medical treatments and manage affordability may be inadequate** to cope with the growing number of gene therapies being introduced. To overcome this hurdle, stakeholders should collaborate on policies that create pricing and financing structures that maximize consumer access to these technologies while incentivizing further research and innovation". ACI (2019).

[18] Naturally, the percentages of the instalments may be variable and not fixed, as for the case of accelerated amortisations, to reflect prepayment of costs in the initial years or higher post payments in the final years, to appropriately consider the success and potential efficacy of the therapies.

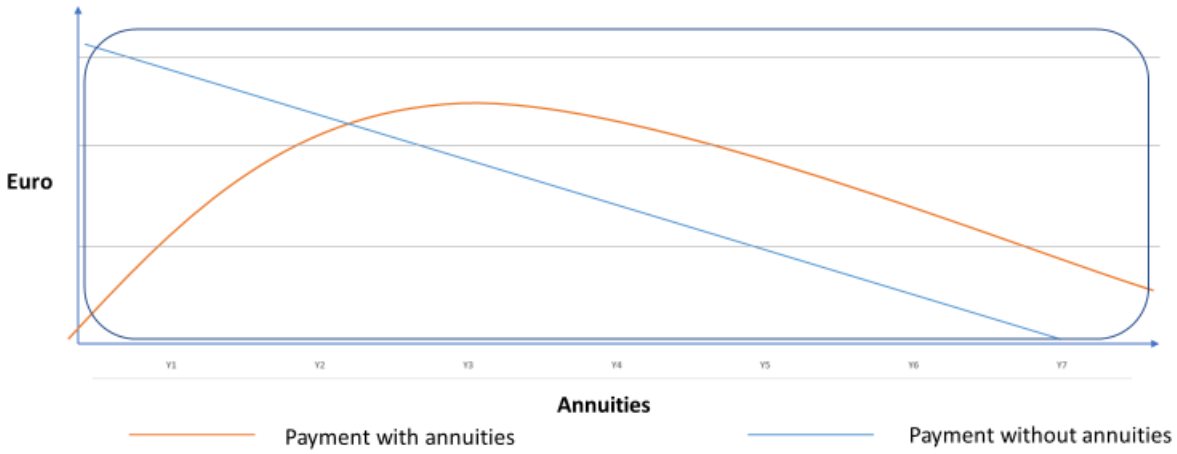
d. the national healthcare system risks only the payment of the upfront percentage. The producer companies risk the remaining percentage of the cost of the drug in the case that it is not effective for that specific patient;
e. naturally, when the therapies are adopted, we will need to study, define and share the criteria and procedures for determining the efficacy of those therapies over time and the appropriate revisions.

*Table 6. Instalment payment model*




**This model would allow the NHS to bear the costs of a new therapy over time, as in the case of chronic therapies**; therefore, in line with the benefits obtained in terms of health and could allow the NHS to allocate health resources in the short to medium term to the resolution of further treatment needs ("unmet medical needs") (see Table 7.). The percentage of expenditure that is subject to accrual for the purchase of ATMPs by the NHS could be considered a substantially investment expenditure and therefore be as such accounted for.

*Table 7. Long-term budgetary impact*




In studying the proposed Annuity Model, the following should be considered:

- the importance of identifying very clear and distinct KPI/clinical end points for payment by result (for example, survival or parameters that can be measured and determined objectively simply in clinical practice);
- the determination of the model must include a definition of the type of pathology treated by the ATMP and the cost of treatment (pharmacological therapies and other forms of assistance) for alternative therapies already available;
- the instalments must be real annuities, and each must fall due in a different accounting year. It is true that the current system uses the accrual system (based on annual spending commitments), but the logic of instalments makes deferred payments very useful for the final payer, even in the current situation;
- the introduction of AMPTs should take place in a context involving a careful evaluation by appraisal bodies of the impact, in terms of **benefits, on the direct and indirect costs of the therapies in question**. The medical cost and pharmaceutical cost must also be correlated (avoidance of silo logic).

*5.2 The impact of the Annuity Model on pharmaceutical governance*

The Annuity Model appears to be compatible with the reference legislative framework, in terms of regulatory aspects and governance, and with the principles of the Procurement Code. Specifically:

a) in regulatory terms and in line with price and reimbursement agreements, a contract term of 24 months or even only 12 months would not be an obstacle to

deferred payment of the price. Indeed, in such a case, notwithstanding the original term of the contract, only the obligation – moreover for the hospital – for deferred payment of the price would remain in force and survive the dissolution of the contract, as implemented upstream in the corresponding supply contract;

b) in terms of governance, also, payment of the deferred price would not seem to conflict with an annual payback system determined on the basis of market share, where, for the purposes of calculating that share, the price "instalment" for the reference year could be calculated and not the entire price. Similarly, for innovative drugs, the base would only be calculated in terms of the price instalment payable for the reference year and only that price instalment would be used to determine the market share (i.e.: of turnover) and the quantification of the company budget and corresponding payment;

c) in the absence of methodologies adopted to date by the AIFA, within the meaning and for the purposes of new governance and, therefore, associated with the allocation of market share and calculation of the corresponding payments, it is not however possible to exclude the potential emergence of critical factors in relation to the implementation of deferred payment models over the years;

d) in terms of hospital supplies, where a single drug is available for a given indication, the corresponding supply to institutions would be based on a contract concluded following direct negotiations with the reference company and that contract could easily lay down terms for deferred payment over time and in tranches;

e) similarly, deferred payment over time would not conflict with the principles of the Procurement Code, in cases where a drug must be supplied on the basis of an award process and a tender procedure. Specifically, this method would not already apply on the basis of a provision in the tender documentation, but rather because it is inherent in the reimbursement conditions for the drug and, therefore, stipulated upstream in the price and reimbursement agreement concluded with the AIFA, through natural integration of the procurement conditions, along the lines of what happens for MEAs. This is of course subject to the possibility that tenders may in the future include possible terms for invoicing and payment that are differentiated for specific types of drugs.

## 6. A possible solution for distribution of the price between current expenditure and investment costs

The fundamental point, therefore, is the distribution of the price paid for the drug into two separate amounts. The first amount should incorporate the component to be considered for deferred use, and thus the amount to be posted as investment expenditure. The second should represent the amount to be posted as current

expenditure, and therefore included in the national accounts for the year in which payment is actually made.

For this purpose, it is essential to identify robust criteria to enable a clear, unambiguous distinction between these two amounts, for which the accounting treatment has significant repercussions for the Government's balance sheet.

The approach should therefore start with the determination of criteria that identify the expenditure associated with ATMPs as an investment applicable to more than one year. To identify the criteria, the following elements should be taken into account:

- the time distance measured in years between the point of initial payment and the final point when the benefit will be enjoyed;
- to determine this period, the durability of the beneficial effects of the treatment must be measured;
- to measure durability, it is possible to: (i) use the evidence emerging from product registration studies that, in general, refer to relatively short time horizons (between one and three years on average); (ii) take into consideration all subsequent data (including real world data) collected by the company and from independent research on the duration of the effects; (iii) consider the observation period considered to be sufficient by the regulatory authorities for pharmacovigilance purposes; (iv) use an evaluation of the characteristics of the mechanism of action of the therapy that demonstrate its "curative" or "transformative" nature with the corresponding implications in terms of duration and significance of the health effects;
- lastly, it is necessary to identify an index of certainty/uncertainty of durability corresponding to the "discount rate" to be applied to the net economic benefit value (emerging costs – ceasing costs) spread over the hypothetical period of durability.

The identification of the correct starting discount rate is subject to a series of variables including the time horizon, but also the socioeconomic context in which the analysis is conducted[19].

The discount rate, in this case, can be defined using the rate normally used in pharmacoeconomic analysis[20], corrected to take into account the level of uncertainty calculated using the method described above. Uncertainty will tend to increase with the reduction in the robustness of the evidence available at the time when the degree of reimbursement is determined and, therefore, the negotiated agreement is concluded and, consequently, this will lead to a higher discount rate.

[19] See in this regard, Attema AE, Brouwer WBF, Claxton K. Discounting in Economic Evaluations *Pharmacoeconomics*. 2018 Jul;36(7):745-758.

[20] Nationally, the Guidelines for Economic Evaluations of the Italian Association for Health Economics (AIES) suggest that benefits and costs (or net benefits) should be discounted by a percentage of 3%/year (as shown by the study by Attema et a., see footnote 16).

For example, considering a period of durability of the effect estimated as 40 years, and the availability of evidence that testifies to the durability of the effect for example for ten years (such as ten years disease-free living for the first patient treated and evaluated) and where the mechanism of action of the drug promises to "cure" the morbid condition, the first nine years are discounted at a rate of 3% (value stated in the AIES guidelines), and from the 11th to the 39th years the rate will increase progressively until it reaches 100% in the 40th year.

It will therefore be possible to distinguish the component of expenditure that will refer to the first year and will be considered as "current" from the component to be considered as investment expenditure. The proportion will obviously be variable and the amount of "current" expenditure will increase progressively as the uncertainty associated with the durability of the effect over time increases.

## 7 Accounting and balance sheet criteria

It is therefore clear that to guarantee access for patients to advanced therapies, it will be necessary to define an innovative approach to determining price and reimbursement practices and, in any case, profound modifications to the mechanisms for supply, reporting and funding of medical treatments. The various alternative methods of funding have different objectives: reducing the total cost of these therapies, identifying accounting procedures that can be shared as fairly as possible between governments and pharmaceutical companies, increasing opportunities for access for patients and, above all, distributing the cost of therapies over time, in economic and financial terms, in a manner that is efficient, appropriate and sustainable[21].

As we have seen, the most important aspect of ATMPs is that, **because there are clear elements of an expenditure with benefits deferred over time, they can in fact be considered investment expenditures.** The prolonged distribution of benefits over time suggests a need to identify an economic and accounting distribution of costs that is more harmonised and in line with the achievement of the benefits. **ATMPs generate a clear asymmetry between the payment of the costs and the emergence of the benefits**: the former are concentrated essentially in a specific year, the first year, in which the financial requirement for the expenditure emerges and needs to be covered in the budgets. The latter are, however, clearly multiannual.

[21] See Hercher-Prince (2019) "One-time treatment is a common theme—and, indeed, often the raison d'etre—of gene- therapy treatments. Gene-therapy treatments **may drastically alter our medical and reimbursement systems because they have the potential to be one-time, curative treatments**. However, for the same reason, a **pharmaceutical company must recover all of its per-person investment in research, development, and cost of treatment from a single payment rather than spread them over time**, as in the typical model of ongoing treatment or lifetime care".

Traditional medical therapies and medicinal products are evaluated at an upfront cost and using a cost/efficacy approach. Reference is generally made to the patient population and estimates are often based on expenditure requirements committed in individual budget years. The development of medicine, medical research and life sciences based on DNA will result in the emergence of more therapies with a systematic impact in the medium/long term. A traditional cost/effect criterion, and above all one applied solely in terms of annual budget, therefore appears inadequate and incompatible with the Annuity Model analysed above (which, as we have seen, would make it possible for the national healthcare system to support the costs of a new therapy over time and, therefore, in line with the benefits obtained in terms of health, thus making it possible for that system to allocate resources in the short and medium term to resolving unmet medical needs), and therefore requires the definition of a new approach.

The use of a budget impact analysis seems to be able to offer interesting prospects. However, this approach must be synchronised with the budget of the healthcare systems – and more generally public budgets – which are based on annual expenditure commitments (accruals method). In the case of ATMPs, we therefore need to adopt a view based on the time horizon during which the economic and financial impact of the various expenditure items will be felt, and that is multiannual. An appropriate compromise must be found between the annual dimension of budgets and the accrual of costs and benefits in the healthcare sector, which clearly exceeds a period of just one year[22].

The current budget procedures are very clear-cut and do not envisage exemptions from the budget principle of accruals and budget commitments[23]. The rules for preparing the national budget require that the cost of a medicinal product or therapy be posted in full in the budget for the year, on the basis of the budget commitments defined. That expenditure may even be settled and paid in subsequent years, but the total amount must be posted in the year in which it is committed. The accruals principle identifies the criterion used to allocate the costs and the effects of the activities of the various public administrations undertaken in each year (accounting year), irrespective of financial and cash movements. The consequence of the operations must be posted in the accounts and assigned to the financial year to which those operations relate, not to the financial year

[22] "*Budget impact analyses should be presented for **the time horizons of most relevance to the budget holder**. They should accord with the budgeting process of the health system of interest, which is usually annual. The framework should allow, however, for calculating shorter and longer time horizons to provide more complete information of the budgetary consequences. A particularly useful extension of the time horizon for a chronic health condition is to reflect the impact that might be expected when a steady state would be achieved if no further treatment changes are assumed. This will vary with the condition and with the impact of the new intervention, but **will generally be longer than the current budget period because of costs and benefits that accrue over time.** Although time horizons that go beyond a few years are subject to considerable assumptions, they may in exceptional cases be required to cover the main implications of the health condition (e.g., some vaccinations). In any case, results should be available disaggregated over time in periods appropriate to the budget holder (e.g., annual, etc.). Hence, to be most useful, the output must be the **period by period level of expenses and savings** rather than a single* "net present value", Mauskopf et al. (2007).

[23] See Law No 196 of 31 December 2009, which governs the criteria used to prepare the government budget, and Law No 243 of 24 December 2012 and Law No 163 of 4 August 2016, which update and review those criteria.

in which the corresponding financial movements will be shown (which is recorded in the cash-flow statement).

The Government and other public administrations have two balance sheets: **the financial balance** sheet shows the legal obligations (expenditure commitments) created in a given year, while the cash-flow statement records the actual outflows (payments). The accruals principle requires that transactions be recorded in the period in which they are created, irrespective of when payment takes place. However, **the cash-flow principle** only considers the costs and revenues for which there is a financial impact (resulting in a monetary movement). Inflows and outflows are recorded at the time when the conditions giving rise to the economic effects of the expenditure decision occur, and thus when the commitment is effectively made, irrespective of the point when the payment actually takes place. This procedure and the unique, annual nature of the Government's balance sheet do not preclude the possibility that a payment staggered over several years might per se be admissible[24].

The bulk of healthcare expenditure is considered to be current. This is clearly indisputable for many expenditure items – personnel, salaries, etc.. But it is even clearer that an increasing share of therapies and new medical protocols are assuming visible characteristics of expenditure for investment. The spread of the COVID-19 epidemic has now demonstrated clearly that healthcare is a fundamental investment for any country and determines its sustainability and its economic and social success. A growing and substantial portion of healthcare expenditure shows clear characteristics of investment, able to generate benefits over a multiannual time horizon. This significant component of investment in healthcare expenditure is obviously not easy to estimate. As indicated in the public accounting standards (see RGS 2019), investment expenditure identifies all expenditures that have a direct or indirect effect on the formation of national physical, human and resource capital. In the current definition, public investments are represented by the "*volume of expenditures that the Government, the regions and the public administrations incur with the objective of increasing the stock of physical and technological capital available to the country*".

As we know, the distinction between current expenditure and capital expenditure is not easy and simple and is a question that economists have been debating for decades. In

[24] As stated in the General Accounting Standards (RGS) (2019), the resources appropriated in the expenditure estimates are committed using a process broken down into four successive phases: commitment, validation, authorisation and payment. "The allocation of financial resources made available by the balance sheet estimates has some room for flexibility, which make it possible to combine the management and implementation function with the authorising nature of the budget law. These margins were established by Law No 196 of 31 December 2009 and other related legislative sources. Other than by potential new financing laws or by legislation introducing new levies, which must be approved by Parliament during the financial year, the forecasts imposed by the budget law may be modified using other legislative or administrative instruments. The Public Finance and Accounting Law stipulates that the budget balancing law is the principal legislative instrument used to act on the balance sheet during the financial year. That law sets out the values for variations – compensatory, between programmes within a single mission – in the financial balance sheet and cash-flow statement, which may modify the estimates only for the current financial year."

general terms, we can say that the distinction remains complex and controversial, because it is essentially based on a determination of the different durations of the effect generated by good and services obtained through various expenditures. Indeed, on the basis of this distinction criterion, expenditures are current if they relate to the purchase of goods and services for which the "*economic utility is used up in the accounting year in which the expenditure took place*". Capital expenditures, however, are those for which this effect lasts for more than the year concerned and is passed on over several years.

While we have provided evidence in the previous paragraphs of the intrinsic characteristics of advanced therapies that enable their classification, at least in principle, as investments, from a purely Government accounting point of view, can ATMPs be considered an investment expenditure? And how much expenditure should be committed in the year and how much in other periods? In a certain sense, ATMPs can be likened to gross fixed capital formation, namely the category of acquisitions of movable property, machinery and equipment (the budget item to which advanced therapies can be allocated is equipment).

The need to consider the investment component of certain public expenditures is clear and already emerged some time ago in discussions on public accounting and in the harmonised national accounts system among countries adopted by the UN (SNA) and in the European Union. For example, it has been recognised that a portion of expenditures for defence are primarily expenditures for investments and not current expenditures. It is clear that public accounting procedures must be better harmonised and shared among the various nations. It may also be necessary to conduct an extensive review of the public accounting criteria used in procedures to calculate national income and national statistical accounts.

Of course, raising this aspect should not be interpreted as a clever expedient for circumventing the limits and public finance constraints of the balance sheets of modern states. Within the EU, for example, there has always been scepticism about exclusion of expenditure for investment from the criteria in the Stability Pact and public accounts supervision, not only because of the difficulties involved in estimating this, but especially because of the fear that the difficulty in defining and determining the characteristics of expenditures for investment would stimulate the various nations to practice forms of creative accounting. It is clear that expenditure for education and, even more, healthcare expenditure has an indisputable investment component, given the effect that they can have on available human capital and productivity.

It is also appropriate to highlight the fact that, in addition to the increasing adoption of multiannual budgets, for policy and budget programming purposes, and simply for the budget in general in many public budgets, the last two decades have seen the widespread use of various different innovative estimation methodologies based on forms of generational accounting, which evaluate the effects of expenditure and taxation decisions not just for the financial year but also in terms of the effects over the life cycle, on the

basis of an estimation of the effects on various age cohorts[25]. These exercises are generally performed for pension systems and environmental policies, with an estimation of the economic effects of certain budget choices for one or more generations. A general spread of these exercises does, however, seem unlikely: given the time inconsistency in estimating the effects of specific policies, over the life cycle of various age cohorts, governments are interested in considering only the short- and very-short-term effects of budgetary choices and expenditure decisions, associated with the likelihood of re-election. However, it is clear that health and the estimation of the effects of healthcare policies on the life-cycle profiles of individuals – for specific age cohorts – is a central issue, if not the most important, of the effects of public policies over time, which can prove the economic and social sustainability of alternative economic choices and different life models.

Yet this time, above all because of the effect of the global COVID-19 epidemic we are experiencing, a different approach, one that is more realistic and appropriate, seems to be necessary and essential. Advanced therapies are different from traditional medicines, aiming to provide a definitive cure for various pathologies with systematic and lasting effects. An improvement in living conditions tends to have obvious effects on human capital and thus on capital stock.

Legislative Decree 118/2011 (so-called "Decree 118") has considerably innovated the financial and economic accounting rules of the Regions, Local Health Authorities, hospitals and Ircss. The aim is to achieve greater control of public finance balances by the central government, with the provision of precise economic, financial and equity rules for the preparation of financial statements and the evaluation of expenditure and revenue. This step was mandatory in order to avoid situations of financial instability of decentralised entities, especially in the health sector, which has been characterised by huge deficits and considerable budgetary imbalances.

Decree 118 clearly provides for the assimilation of Local Health Authorities and hospital companies to a private operator with the extension to these entities of the economic asset accounting: beyond the financial accounts, it provides for the preparation of a profit and loss account, a balance sheet and a multi-annual budget to give full account of the budgetary evolution of these entities and to put the various balance sheet items under the control of the Mef. It has therefore been provided for the definitive assimilation, with a few exceptions, of the financial statements of the Local Health Authorities and hospitals to the civil law principles for the preparation of financial statements. Therefore, a number of precise rules have been introduced that provide for a precise and constant monitoring in real time of the trend of the budget balances of health institutions and their effects on public finance balances.

The provisions of Decree 118 also provide for the preparation of consolidated financial statements in such a way as to ensure full reconciliation and "reconciliation between the

[25] See Auerbach-Kotlikoff (1999).

items written and accounted for in terms of economic and financial accounting and those recorded in terms of financial accounting".

Article 25 of Decree 118 provides for an annual economic budget in an explicit manner: "1. The bodies referred to in Article 19(2)(b)(i), where the conditions laid down therein are met, and (c) shall draw up an annual economic budget, consistent with the health and economic-financial planning of the region. 2. The annual economic budget shall include a projected income statement and a projected cash flow plan, drawn up in accordance with the income statement and cash flow statement formats provided for in Article 26. A detailed income statement shall be attached to the forecast profit and loss account, in accordance with the EC format set out in the Ministerial Decree of 13 November 2007 and subsequent amendments and additions. 3. The annual economic budget is accompanied by explanatory notes and the investment plan".

Article 26 also provides for the financial statements and the financial statements of the NHS entities:
"1. They comprise the balance sheet, income statement, cash flow statement and notes [...].
2. The financial statements drawn up by the entities referred to in Article 19(2)(d) shall be submitted to the Board of Directors of the entity for approval.
3. In order to give a uniform structure to the items in the annual economic budget and the annual financial statements, as well as uniformity to the values included in these items, the entities referred to in Article 19 (2) (c) and (b) (i), where the conditions laid down therein are met, shall draw up the annual financial statements according to the specific layouts set out in Annex 2, which form an integral part of this legislative decree. The entities referred to in letter d), paragraph 2, of Article 19 shall adopt the same financial statement formats, adapting the notes to the financial statements and the report on operations to the specific features of their operating area".

The most essential point, however, comes with art. 56 of Legislative Decree 118/2011 where the aspect that is most relevant for the analysis conducted herein appears. The article states that for expenditure commitments: " 1. **All legally perfected passive obligations, from which expenses for the region derive, must be recorded in the accounting records when the obligation is perfected, with allocation to the year in which the obligation matures, in accordance with the procedures provided for by the applied principle of financial accounting in Annex no. 4/2**. Expenditure is recorded in the accounting records even if it does not give rise to actual cash movements. 2. The commitment shall constitute the stage of expenditure at which the completion of a passive legal obligation is recognised, and the reason for the debt, the amount to be paid, the creditor, the specification of the obligation entered into on the budget appropriation and the due date shall be determined. 3. Expenditure commitments shall be entered into within the limits of the respective appropriations entered into in the budget appropriation and booked to the financial years in which the obligations are due.

Therefore, an expense is in fact committed only when the legal obligation is "completed" and is charged "to the year in which the obligation matures". The effect of this rule is that it will no longer be possible to refer to the current year "legal obligations that have not matured in the same year"[26].

Therefore, the provision provides that the entire amount of the amounts allocated and committed, regardless of their financial manifestation, is entered in the financial statements in the year in which the commitment is completed. This provision, with the provision of a precise guideline on the accounting of current expenditure, should make it possible to have greater control over expenditure and the effects on public finance balances for the decentralised bodies and the central state.

The question is, however, how to correctly account for and budget investment expenditure. The tenor of the **rule seems to confirm that the recording of investment expenditure should not take place in the year in which the financial cover is identified, but follow the rule of the state of progress that will gradually mature, typical of investment expenditure**. The objective of the rule seems clear: that is, to minimise the formation of passive waste and to make the public budget more transparent.

The crucial point for ATMPs is therefore whether they can be considered as an investment expenditure, which produces benefits over time, and therefore how can these expenditures be correctly assessed and accounted for.

It could be argued that a large part of medical products, medicines and treatments may in theory have an investment expenditure characteristic. An anticoagulant (or aspirin itself) or a blood pressure medication certainly has systemic and long-term effects on patients' health - and therefore theoretically could have the aspects of an investment. However, it is quite clear that there are specific advanced medical protocols and therapies (from vaccines to ATMPs) for which the investment element is much more obvious and indisputable. In the case of a blood pressure drug, the long-term effect is produced after a constant and prolonged intake for a long time; and in any case the systemic effect on health is produced with the use of many other medical, social, dietary and environmental factors that are difficult to distinguish and isolate. Finally, the cost of these drugs is definitely very low, they are characterized by a low price and with the de facto irrelevance of the size of research and development and a completely different audience of treatable patients. So even if systemic effects were acknowledged, they have only a small investment component and are close to the consumption of a common drug.

Instead, gene therapies have very specific and different economic and industrial characteristics. In the case of ATMPs, the cost of R&D, the systemic effect easily ascertainable on patients' life prospects and on QALYs; the effects they have on patients' individual productivity and on the general productivity of the economic system; these

[26] Corrado (2016).

therapies also refer to a very restricted audience because they deal with very limited pathologies.

It should be noted, however, that the R&D expenditure underlying ATMPs is considered in ESA 2010 as investment expenditure, rather than as intermediate costs as was the case with ESA 95, as it contributes to the accumulation of production capacity through intangible fixed assets.

On the basis of the above considerations, and considering that ATMP expenditure can be effectively assimilated and therefore treated in the same way as fixed investment expenditure, the accounting rules for the three public finance balances are as follows.

The impact on the net balance to be financed, which takes into account **the legal (financial) competence**, corresponds at the forecast stage to the authorisation of expenditure, i.e. the allocation provided for by specific regulatory provisions, and at the management stage to the accounting commitment.

For the purposes of net indebtedness, reference is instead made to the **accounting competence**, a principle which in this case (since it concerns expenses relating to gross fixed investments) conventionally applies the cash criterion for the reasons explained below; this criterion is also valid for requirements; this criterion is also valid for needs, i.e. it refers to the actual annual disbursements that are expected to be made for the implementation of the intervention, even if, as far as debt is concerned, according to the ESA 2010, gross fixed capital formation is recorded when ownership of the assets is transferred to the institutional unit that intends to use them and consequently the amount to be recorded corresponds to the actual increase/decrease in the value of the investment asset.

It was also agreed that - due to the lack of information on the actual time at which this effect occurs - the recording of investments on net debt is based, by convention, on actual payments, as they are more representative, compared to the accounting commitment, of the increase in capital stock during the reference period.

Therefore, the conventional criterion applied for fixed investments, whereby the impact on net debt is represented by payments made on the basis of the progress of work (SAL), i.e. the part of the work or intervention carried out, can also be extended to ATMP-related expenses with the same impact on net debt and requirements, corresponding to payments related to the benefits of the treatment to which the patient is subjected.

Since the cost of the therapies is considerable and concentrated in the short term, while the effectiveness of the therapies and the related benefits for the patients are seen over a longer time horizon, it is plausible that agreements implemented by administrative or regulatory acts, between the public payer and the producers of advanced therapies, can be implemented, in order for the accounting commitment (**legal competenxe**) to follow the payment due, i.e. the cash criterion - i.e. in the case of ATMP expenditure, which can

be classified as gross fixed capital formation (GFCF), the **accounting competence**, which is usually applied for the impact on net debt, is conventionally replaced by the cash criterion; in this way the timing of the authorisation of expenditure from the public budget would be substantially in line with that of the effects in terms of therapeutic benefits on patients.

In this sense, and in order to strengthen this alignment, an **ad hoc rule with a specific multi-year expenditure authorisation could be building**, so as to bring the time of the accounting commitment, typical of the legal competence, closer to the actual payment (the cash criterion), which in the case of gross fixed investments represents the criterion applied for the economic competence. This approach also appears to be in line with the accounting principles as amended by the implementing decrees of the accounting and public finance reform of Law 196/2009: **Legislative Decree 116/2018**, containing additional and corrective provisions of Legislative Decree 90/2016. With the aforementioned Legislative Decree 116 - art. 7, paragraph 1, letter a) - the accounting principles contained in the original attachment 1 to Law 196/2009 are essentially reformulated in Annex 1 to the Decree, in order to make them consistent with the new approach outlined with the reform and, in particular, with the **provision to strengthen the function of the cash balance sheet**. With a view to coordination, the general accounting principles of the local authorities annexed to Legislative Decree 118/2001 have also been taken into consideration.

The most important changes concerned the principle of financial (legal) competence and the principle of economic competence[27]. Another important decree implementing the reform of Law 196/2009, **Legislative Decree 93/2016**, which **revised the notion of accounting commitment in order to bring the moment of legal competence (commitment) closer to that of cash (payment), is included between the two legislative decrees mentioned above.**

**Legislative Decree 29/2018**, which came into force subsequently, introduced corrective and supplementary amendments to Legislative Decree 93/2016 for the application, from January 1, 2019, of the new **concept of accounting commitment**, according to which the legally perfected obligation is entered in the accounts for the years in which it becomes due (multi-year commitment to be due). Ultimately, **from 2019, the commitment must be entered into in the financial year or years in which payments are expected to be made in accordance with the contractual or regulatory deadlines**. As a result, there is a rapprochement, also reinforced by the ad hoc rule mentioned above, between the time

[27] The accounting competence principle has been modified to take into account, among other things, the specific characteristics of the State budget, which is mainly characterised by non-saleable production activities and significant transfers to other entities within the public perimeter and the rest of the economic system. The financial competence principle has been reformulated taking into account the specific accounting and public finance rules that govern the State budget, including regulatory innovations, including those concerning the allocation of commitments to the financial years in which the obligation matures. On the activity carried out for the implementation of the reform of Law 196/2009, reference should be made to the individual reports on the state of implementation of the reform of accounting and public finance presented by the Minister of the Economy and Finance attached to the Economic and Financial Document.

of the commitment and the time of payment which, in the case of ATMPs, as investment expenditure, essentially leads to an alignment between legal competence and economic competence with an essentially uniform effect on the three balances, also in terms of financial coverage.

## 8. Conclusions

The possibility of **building an ad hoc rule with a specific authorisation for expenditure of a multiannual nature with aligned legal competence and economic competence, including in terms of financial coverage, has been considered**. This is in fact already possible with the existing rules. Of course, some specific solutions can also be envisaged.

### A. Establishment of a dedicated Fund

A possible solution is to build an ad hoc fund to which those therapies with the following characteristics can access:

a. have an efficacy profile that substantially transforms the natural history of the disease (transformative) or is curative;

b. generate therapeutic benefits in the long and very long term against a treatment that often takes place "one-shot", generating a misalignment between the cost incurred and the enjoyment of the benefits;

c. generate additional benefits in terms of recovery of productivity at work over long periods of life which is improved in its psychological, relational and social aspects;

d. generate impacts on other levels of care in the healthcare system as they imply the involvement of hospital resources in the care process;

e. involve co-responsibility for treatment outcomes between the pharmaceutical industry and the healthcare system that intervenes with expertise and other technologies to support the treatment process.

The assessment of the existence of these characteristics could be carried out through the procedure for the updating of the LEAs, which provides for the evaluation of technological innovations through an HTA approach that, suitably adapted, appears suitable to analyze the multiple facets of the value associated with therapies whose characteristics have been outlined above.

From a technical accounting point of view, this Fund should provide for the recognition of the investment expenditure characteristic and the application of the accounting procedures described above. This ad hoc Fund may provide for the advance allocation of specific amounts and allow for a more appropriate evaluation of the distribution of benefits over several years[28].

[28] The special funds, once their amount has been determined by the financial authority, are used, through the enrichment of pre-existing chapters or the creation of new ones, to meet expenditure arising from draft legislation that is expected to be approved during the financial years included in the multiannual budget and in particular those related to the pursuit of the objectives of the financial programming document approved by Parliament. The funds are distinguished according to whether they are intended to finance current or capital expenditure.

**B. Study a different financing formula and with other parties**

First of all, as in some foreign experiences, the Italian government[29] could make a dedicated bond issue and ask for resources on the market (both directly and through Cdp): *"the government (or another third party) issues loans to payers to fund the upfront bill, and then the health care payer pays instalments over time, in line with realization of the benefits. An example of this type of mechanism can be seen in Spain, where the national government announced low-interest loans for regional payers to fund high cost HCV therapies.*

*The possibility of involving a third market player in the construction of the financing and cash flow sharing mechanism could be explored. "In some instances, amortization could be combined with a third party absorbing the risk. For example, Montazerhodjat et al., (2016) proposed that hedge funds are well placed to provide loans for high cost therapies".*

Another hypothesis is that institutional investors (pension funds, pension funds, insurance companies, foundations) could be involved in the financing of an ad hoc private fund or a dedicated issue by a third market player.

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[29] As proposed in Icer (2017).