AIX-MARSEILLE UNIVERSITE

ECOLE DOCTORALE DES SCIENCES DE LA VIE ET DE LA SANTE

UNITE DE RECHERCHE: EA3279

THESE

présentée pour obtenir le grade universitaire de docteur

Discipline : Pathologie humaine
Spécialité : Recherche Clinique et Santé Publique

Eve HANNA

Les thérapies innovantes:
Une révolution médicale et un Tsunami financier

Advanced Therapy Medicinal Products: Medical Revolution and Financial Tsunami

The need for new pricing policies to ensure the sustainability of the healthcare insurance

Soutenue le 12/12/2017 devant le jury :

Isabelle DURAND-ZALESKI	URC ECO Ile-deFrance	Rapporteur
Guy JADOT	Université de Lyon 1	Rapporteur
Benoit DERVAUX	Université de Lille 2	Examinateur
Bruno LAVIOLLE	Université Rennes 1	Examinateur
Pascal AUQUIER	Aix Marseille Université	Co-directeur de thèse
Mondher TOUMI	Aix Marseille Université	Directeur de thèse

Résumé

Les médicaments de thérapie innovante (MTI) est une classe hétérogène de produits biopharmaceutiques qui englobe les thérapies géniques, les thérapies cellulaires somatiques, l'ingénierie tissulaire et les produits combinés de thérapie innovante (cellules ou tissus associés à un dispositif médical). Ces thérapies sont très prometteuses, elles ont un potentiel de guérir des maladies chroniques avec des importants besoins médicaux non-satisfaits. Les industriels demandent des prix très élevés pour les MTI, mais les contraintes budgétaires imposent aux gouvernements de maintenir la stabilité ou même réduire les dépenses de l'assurance maladie.

Les objectifs de la thèse étaient d'identifier le nombre de MTI en développement, d'évaluer prospectivement l'impact financier que produiront les traitements innovants et de rechercher de nouvelles modalités de paiement des MTI pour aider les décideurs publiques à anticiper l'impact des MTI à court et moyen terme sur le budget de l'assurance maladie.

Dans le premier chapitre, une revue sur la définition et la réglementation des MTI est présentée. L'aspect règlementaire est détaillé : les données exigées dans les phases de pré-autorisation ainsi que la procédure d'autorisation de mise sur le marché et les exigences de surveillance post-autorisation. Les défis qui font face aux MTI sont également discutés ceci au niveau de la recherche et développement, au niveau clinique et au niveau de l'accès au marché de ces thérapies.

Dans le deuxième chapitre, le nombre de MTI en développement sera évalué par le dénombrement des essais cliniques des MTI dans 3 bases de données internationales, et par la détermination de la probabilité de discontinuation des essais cliniques des MTI. Cette étude a montré le grand nombre de MTI en développement et susceptible d'arriver sur le marché.

L'impact budgétaire des MTI est évalué dans le troisième chapitre. Des modèles de Markov ont été développés pour 3 maladies : Alzheimer, Parkinson et l'insuffisance cardiaque. Ensuite, l'impact des MTI dans 35 maladies sera estimé à l'aide des hypothèses. Cette section montre que les prix élevés des MTI seront inabordables, les payeurs ne pourront pas payer le prix de tous les MTI à l'avance.

Une identification des modèles de paiement des thérapies innovantes est effectuée via une revue de la littérature. Ces modèles ont été évalués et discutés durant une réunion d'experts puis un modèle de paiement optimal pour les MTI est suggéré.

A la fin, des recommandations stratégiques sont présentées pour aider les industriels et les décideurs publiques à assurer l'accès des patients aux thérapies innovantes tout en maintenant la pérennité de l'assurance maladie et évitant la faillite.

Abstract

Advanced therapy medicinal product (ATMP) is a heterogeneous class of research driven biopharmaceuticals encompassing gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (sCTMPs), tissue engineering products (TEPs) and combined products (cells or tissues associated to a medical device). ATMPs have promising potentials for curing many chronic and disabling diseases with high clinical unmet needs. This clinical potential is usually associated to a high price of ATMPs claimed by manufacturers. Nowadays, high-cost ATMPs started reaching the market while payers are trying to cut the health expenditure by using cost-containment strategies due to budget constraints.

The objectives of this thesis were to identify the magnitude of the ATMPs pipeline, to assess the budget impact of ATMPs and to suggest new funding models for ATMPs in order to help decision-makers to anticipate the hypothetical short and medium term budget impact of such products.

In the first chapter, an overview on ATMPs was presented: the definition of ATMPs, the types of ATMPs, the ATMP regulation in EU, the bodies responsible of ATMPs evaluation. In addition, we detailed the requirements for ATMPs in the pre-marketing authorization phase, the marketing authorization procedure and the post-marketing requirements. Then, the challenges facing the ATMPs were discussed: at R&D level, clinical development level and market access level.

In the second chapter, the magnitude of ATMPs pipeline was evaluated by identifying the number and characteristics of ATMPs clinical trials in 3 worldwide clinical trials databases and assessing the risk of discontinuation of ATMPs trials. A large number of ATMPs are in development (939 clinical trials) and may successfully reach the market. Overall, the results showed that the number of ATMPs clinical trials has been consistently growing over the past 15 years.

In the third chapter, the budget impact of ATMPs that will reach the market was assessed. Markov models were developed to assess the cost-effectiveness and budget impact for ATMPs using 5 efficacy scenarios in Parkinson disease, Alzheimer's disease and heart failure. Then, an estimation of the budget impact of 35 ATMPs was conducted suggesting that an ATMP can cure all patients. We have shown in this chapter that a cost-effective ATMP may be unaffordable; payers will not be able to pay upfront the costs of all ATMPs. The traditional funding models may not be adaptable for ATMPs.

In the fourth chapter, the proposed funding models for innovative high-cost therapies were identified through a literature review, discussed during a consensus meeting and an optimal funding model for ATMPs was recommended.

Finally, health policy recommendations for the stakeholders – patients, physicians, payers and manufacturers – are presented. These recommendations aim to help to ensure patient access to innovation while maintaining the sustainability of healthcare system.

List of Publications

Published:

- Hanna E, Rémuzat C, Auquier P, Toumi M. Advanced therapy medicinal products: current and future perspectives. J Mark Access Health Policy. 2016;4.
- Hanna E, Rémuzat C, Auquier P, Toumi M. Risk of discontinuation of Advanced Therapy Medicinal Products clinical trials. J Mark Access Health Policy.2016;4
- Hanna E, Rémuzat C, Auquier P, Toumi M. Gene therapies development: slow progress and promising prospect. J Mark Access Health Policy. 2017 Jan 1;5(1):1265293.

Accepted for publication:

- Hanna E, Toumi M, Dussart C, Borissov B, Dabbous O, Badora K, Auquier P, Funding breakthrough therapies: a systematic review and recommendation, Health policy journal, In Press.

List of Conferences Presentations

1. Hanna E, Tavella F, Rémuzat C, Auquier P, Toumi M, Market access of ATMPs: Overview and expected challenges, presented at ISPOR 18th European meeting, Milan, Italy, 2015.
2. Hanna E, Rémuzat C, Auquier P, Toumi M, Advanced Therapy Medicinal Products may dramatically impact payers' budget, presented at ISPOR 18th European meeting, Milan, Italy, 2015.
3. Lee D, Hanna E, Hammi El, Rémuzat C, Toumi M, Sofosbuvir: The Failure of Pricing Policies in the European Union, presented at ISPOR 18th European meeting, Milan, Italy, 2015.

4. Hanna E, Korchagina D, Toumi M, comparison of the trends of orphan drugs designations and approvals in the United States and Europe in oncology, presented at ISPOR 7th Asia-Pacific Conference, Singapore, 2016.

5. Hanna E, Rémuzat C, Auquier P, Toumi M, risk of discontinuation of advanced therapy medicinal products clinical trials, presented at ISPOR 7th Asia-Pacific Conference, Singapore, 2016.

6. Hanna E, Zhou J, Cheng X, Dorey J, Aballéa S, Auquier P, Toumi M, Advanced Therapy Medicinal Products for Alzheimer's disease will shrink the national health service budget, presented at ISPOR 19th European meeting, Vienna, Austria, 2016.

7. Hanna E, Dorey J, Aballéa S, Auquier P, Toumi M, Will stem cells for heart failure be the next sofosbuvir issue?, presented at ISPOR 19th European meeting, Vienna, Austria, 2016.

8. Hanna E, Ma F, Cheng X, Dorey J, Aballéa S, Auquier P, Toumi M, Future innovative therapies for Parkinson's disease may question sustainability of our health care system, presented at ISPOR 19th European meeting, Vienna, Austria, 2016.

9. Hanna E, Rémuzat C, Auquier P, Toumi M, Advanced Therapies: Widening the gap between payers and regulators, presented at ISPOR 19th European meeting, Vienna, Austria, 2016.

10. Hanna E, Azaiez C, Auquier P, Toumi M, A new accelerated early access process for diagnostics in France, presented at ISPOR 19th European meeting, Vienna, Austria, 2016.

11. Hanna E, Rémuzat C, Auquier P, Toumi M, Relevance of indirect comparison in HAS assessment, presented at ISPOR 22nd Annual International Meeting, Boston, USA, 2017.

12. Hanna E, Rémuzat C, Auquier P, Toumi M, Gene therapies development: slow progress and promising prospect, presented at ISPOR 22nd Annual International Meeting, Boston, USA, 2017.

13. Hanna E, Rémuzat C, Auquier P, Jadot G, Toumi M, Do French health economics and clinical HTA committees have coherent appraisals of clinical trials? Presented at ISPOR 22nd Annual International Meeting, Boston, USA, 2017.

14. Hanna E, Rémuzat C, Auquier P, Jadot G, Toumi M, Funding of gene therapies In Europe & the United States, Presented at ISPOR 22nd Annual International Meeting, Boston, USA, 2017.

15. Hanna E, Remuzat C, Auquier P, Dussart C, Toumi M., Could healthcoin be a revolution in healthcare?, Presented at ISPOR 20th Annual European Meeting, Glasgow, Scottland, 2017.

16. Hanna E, Remuzat C, Auquier P, Dussart C, Toumi M, Potential funding sources for breakthrough therapies, Presented at ISPOR 20th Annual European Meeting, Glasgow, Scottland, 2017.

Acknowledgements

I would like to express my appreciation to my supervisor Professor Mondher Toumi; you have been a wonderful mentor for me. I would like to thank you for giving me the opportunity to work in the field of health economics, for encouraging me, for allowing me to widen my horizons and to grow as a researcher. I am forever in debt to your priceless advice. I would also like to express my gratitude to my second supervisor Professor Pascal Auquier. I am extremely grateful that both of you agreed to supervise this work and expressed confidence in my research project.

I would also like to thank the examiners, Professor Durand Zaleski, Professor Jadot Professor Dervaux and Professor Laviolle. I am also more than honoured to have these eminent professors in the public examination of this dissertation.

I have many persons to whom I feel appreciation and thankfulness at both academic and personal level. My sincere thanks go to the former dean of the Faculty of Pharmacy at the Lebanese University, Professor Pascale Salameh for encouraging me to do a PhD in France. I am thankful for my colleagues at Creativ-ceutical especially Ms Cécile Rémuzat, Dr Julie Dorey and Dr Samuel Aballéa for their support and helpful critical perspectives throughout the past 3 years.

At the personal level, my warmest gratitude is owed to my dear family. Words cannot express how grateful I am for all of the sacrifices that you have made on my behalf, for your continuous support and encouragement during hardships. I would also want to thank Robert and Mary Kfoury and their sons for being my second family in Paris and for their support. Besides, I thank every person that encouraged me and pushed me to take this step when I was afraid to leave my home country and all my beloved friends in Lebanon and Paris that stood beside me during these 3 years full of ups and downs.

Table of contents

List of Figures

List of Tables

List of Abbreviations

ACO	Affordable Care Organization
AD	Alzheimer's disease
ATMPs	Advanced Therapy Medicinal Products
BI	Budget Impact
BMC	Bone Marrow Cell
CAT	Committee for Advanced Therapies
CATP	Combined Advanced Therapy Product
CDF	Cancer Drugs Fund
CEA	Cost effectiveness analysis
CED	Coverage with Evidence Development
CEPS	Comité Economique des Produits de Santé
CHMP	Committee for Medicinal Products for Human Use
CPI	Consumer Price Index
EC	European Commission
EQ-5D	European Quality of Life-5 Dimensions
ERP	External Reference Pricing
EU	European Union
GCP	Guidelines Clinical Practices
GDP	Gross Domestic Product
GMP	Good Manufacturing Practices
GTMP	Gene Therapy Medicinal Product
H&Y	Hoehn and Yahr
HAS	Haute Autorité de Santé
HCL	Healthcare loans
HCV	Hepatitis C Virus
HF	Heart failure
HI	Health Insurance
HRQoL	Health related quality of life
HTA	Health Technology Assessment
HTA	Health Technology Assessment
IAB	Improvement in actual benefit
ICER	Incremental Cost Effectiveness Ratio
IP	intellectual property
IQWIG	Institute of Quality and Efficiency in Health Care
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MA	Marketing authorization
MAA	Marketing authorization application
mCRPR	metastatic castrate resistant prostate cancer
MEA	Managed Entry Agreements
NHS	National Health Services
NICE	National Institute for Health and Clinical Excellence
NYHA	New York Heart Association
OCM	Oncology Care Model
OECD	Organisation for Economic Co-operation and Development

P4P	Pay-for-performance
PD	Parkinson's disease
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality Adjusted Life Year
sCTMP	Somatic Cell Therapy Medicinal Product
SD	Standard Deviation
SoC	Standard of care
TEP	Tissue Engineered Product
UK	United Kingdom
US	United States
VBP	Value-Based Pricing

Introduction

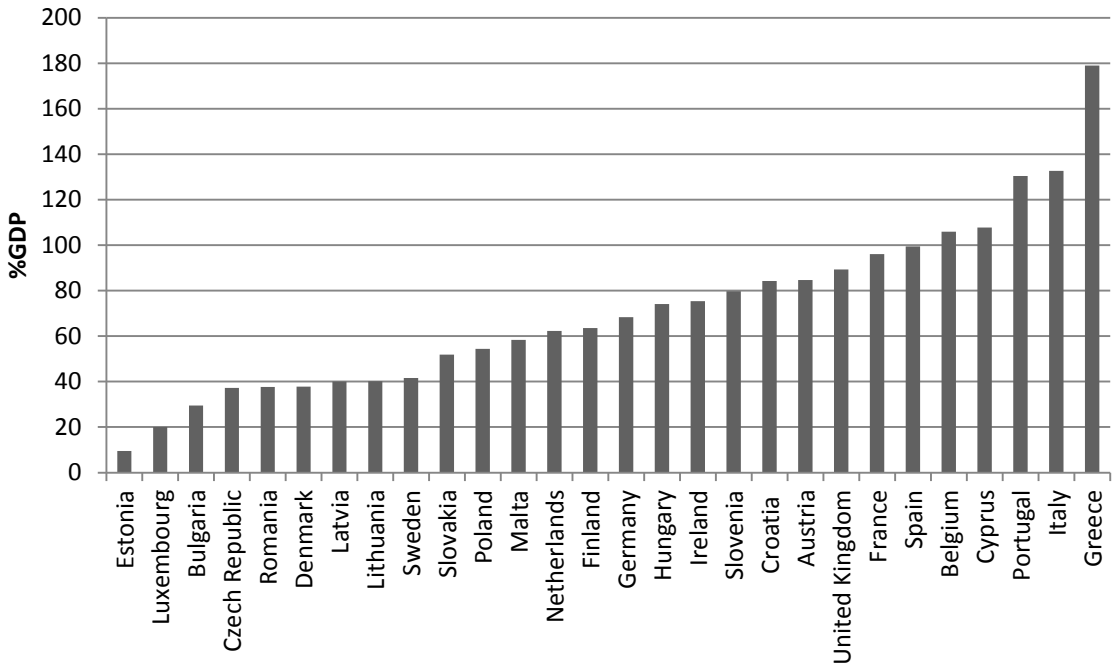
1. Context

1.1. Economic crisis

In 2007, an unprecedented economic crisis hit the global economy, manifested as liquidity shortage among financial institutions. The European Union (EU) entered an exorbitant downturn in the economy (1). In addition, in 2009, Eurozone debt crisis started after Greece's default on its high debts and the situation was aggravated by other EU countries debts (2). The financial crisis has led to an age of austerity and cuts to public spending.

Nowadays, despite economic reforms and austerity, EU is still facing a crisis. According to Eurostat statistics (2016), five European countries have larger debts than their economic output: Greece followed by Italy, Portugal, Cyprus and Belgium with 179%, 132%, 130.4% , 107.8% and 105.9% of Gross Domestic Product (GDP) respectively (3). Therefore, Europe is currently drowning in debt (Figure 1).

Figure 1. Government gross debt as proportion of GDP in Europe



GDP: Gross Domestic Product
This figure was taken from the statistical office of the European Union, Eurostat, responsible of processing and publishing comparable statistical information at European level (3). It shows the importance of the European debts.

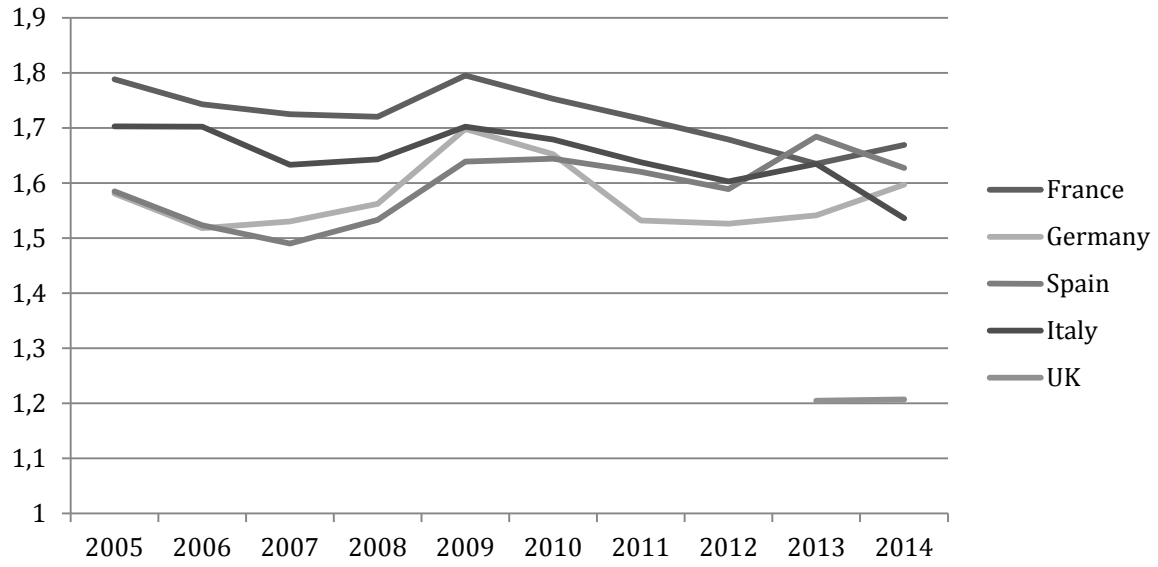
Governments are struggling to reduce public deficits and debts. Indeed, five countries managed to reduce their debt since 2012: Germany, Latvia, Czech Republic, Ireland and Denmark.

1.2. Healthcare expenditure

Healthcare expenditure constitutes an important proportion of GDP; spending on health varies considerably between the different countries; richer countries spend a higher proportion of GDP. The recent statistics showed that Sweden, France, Germany and the Netherlands had the highest current healthcare expenditure relative to GDP among the EU Member States (around 11% of GDP) (4). Figure 2 shows the evolution of pharmaceutical expenditure in the 5 large European countries – France, Germany, Italy, Spain and the United Kingdom (UK) – based on the Organisation for Economic Co-operation and Development (OECD) data (5). A substantial decrease in pharmaceutical spending is noticed after 2009.

According to an analysis published by the German Institute for international and security affairs, OECD countries have a positive healthcare sustainability gap; those countries spend every year a larger proportion of GDP on healthcare (6). In Europe, health care is mainly publicly funded; therefore health sustainability gap will translate in larger public debt.

Figure 2. Pharmaceutical expenditure as percentage of Gross domestic product (GDP) Total, 2005 – 2014 in 5 European countries



Healthcare expenditure in the EU is an unsustainable path. The economic climate has put increasing pressure on governments public spending and many governments are applying cost cutting initiatives. Bending the growth in healthcare expenditure is considered as a key step to reduce public spending and public debt.

1.3. Innovative therapies and high prices

While governments are trying to implement policy reforms in order to trim health care spending, the prevalence of chronic diseases is on the rise and unmet clinical needs are increasing. To fulfill these unmet needs, innovative promising therapies are being developed.

A class of novel biopharmaceuticals called Advanced Therapy Medicinal Products (ATMPs) has emerged, holding promising therapeutic potential to treat chronic and disabling diseases with high clinical unmet needs (7). This class encompasses gene therapies, cell therapies and tissue engineered products.

Those therapies with high value are expected to claim high prices. Indeed, the price of an approved ATMP in Europe, Glybera®, was €1.1million per patient, and another ATMP, Strimvelis® list price was €594,000 per patient (8). Similarly to the ATMPs, nowadays, novel oncology drugs, are reaching skyrocketing prices; cancer drugs introduced in 2014 were on average six times more expensive than drugs introduced in 2000 (9). For example, bevacizumab is used in colorectal cancer and increases life expectancy by 6 weeks costs 5300$ per month (10). Pertuzumab has proven a great ability to treat Human epidermal growth factor receptor 2 (HER2) positive breast cancer but it had a high price ($215,000 per patient (11)).

Many factors drive these high prices claimed by manufacturers: development high costs and moving findings from bench to bedside, competition with older drugs that have a "virtual monopoly" considered as standard of care, and the disease severity and clinical unmet needs (10). Drugs high prices grabbed a lot of attention recently; it has become a major topic in policy discussion and social media. For example, the social group for patients' defense (Ciss, collectif interassociatif de défense des patients) has denounced the excessively high prices claimed by manufacturers for innovative therapies (12).

The issue facing governments that are already operating under budget constraints is to find a balance between ensuring patient access to innovation and maintaining the sustainability of healthcare system. Furthermore, incentivizing pharmaceutical companies to continue to invest in research and development (R&D) by paying high premium prices for innovative therapies is a challenge in a cost-containment environment.

1.4. Sovaldi® case study

An example of the issue of a life-saving therapy that faced many hurdles because of its high price, is Sovaldi® (Sofosbuvir) developed by Gilead. Sovaldi® is a breakthrough antiviral medicine used to treat chronic (long-term) hepatitis C in adults, in combination with other medicinal products (13). The European Commission (EC) granted a marketing authorisation for Sovaldi® on 16 January 2014. Its safety profile was satisfactory in the clinical trials (14). Sovaldi® efficacy has been demonstrated:

- Higher efficacy for the most difficult to treat patients, in particular genotype 1, 4, 5 and 6 patients, cirrhotic patients, pre-transplantation patients and patients co-infected with HIV and HCV (15).
- Genotype 2 patients: a 12-week treatment with sofosbuvir + ribavirin has been effective:
    - SVR12 rates of 97% for treatment-naïve patients (FISSION study) (15),
    - 93% for patients not eligible for, intolerant to or refusing interferon (POSITRON study) (16),
    - For patients who had already received interferon-based treatment (FUSION study), the SVR12 rate with a 12 week treatment course was 82% and 89% with 16 weeks of treatment(16).
- Genotype 3 patients, treatment over 24 weeks with sofosbuvir + ribavirin (VALENCE study) has been effective (17):
    - SVR12 rates of 93% for treatment-naïve patients,
    - 77% for previously treated patients.
- Treatment for 12 weeks with sofosbuvir + peginterferon + RBV triple therapy (LONESTAR-2: phase II study) also appears to be effective (SVR12: 20/24).

Sovaldi® carried a high price tag in the United States (US) of $84,000 or $1,000 a pill for the 12-week treatment (18). After its regulatory approval, Health Technology Assessment (HTA) bodies assessed sofosbuvir and acknowledged its major additional clinical benefit and its cost-effectiveness. But its high price was criticized.

In EU, to face Sovaldi® high price, politicians reacted through an orchestrated media campaign. Gilead, the manufacturer, was called to clarify the gap between the production cost and the price. The most active campaign happened in France where members of parliament and Health Minister multiplied press releases and statements on social media to dispute sofosbuvir price considered as scandalous (19). Gilead

spokeswoman explained that "*despite its clear potential to improve significantly on previous treatment approaches, Sovaldi® was priced such that the total regimen cost is comparable to the previous standard-of-care regimen for genotype 1 patients with hepatitis C"* (18). Controversies appeared; some people considered that Sovaldi® does not deserve the price targeted, and others considered that a "curative" therapy has to be considered in a different way than the drugs with less clinical efficacy (18).

French Health Minister organized a European coalition to control Sovaldi® price. Under tremendous media, political and administrative pressure, the manufacturer accepted significant price decrease, early entry agreement in France and later on in most EU countries. French parliament adopted a law that capped the drug budget expenditure for hepatitis C: If the cap is crossed, companies will have to reimburse the overspent amount. Moreover, Gilead reduced its price and offered a hidden discount and a pay for performance scheme (20). In France, Sovaldi® is 100% reimbursed, its price in 2014 was €498.35 TTC per tablet equivalent to €41,861 TTC for the standard course of 12 weeks, and the price was decreased to €29,302 TTC per 12-week course in April 2017 according to the French official health insurance database.

Following this saga, to ensure drug budget will remain under control, most EU countries issued regulation or law to cap drug budget expenditure for HCV(20).

This situation highlights the difference between cost-effectiveness and affordability. In reality, Sovaldi® was cost-effective, its price was fair based on the Value-Based Pricing (VBP) approach commonly used to set new pharmaceuticals prices (21), but it was not affordable. In the cost-effectiveness analysis (CEA), VBP is established in relation to a CEA threshold. Therefore, sofosbuvir price even if it was cost-effective may have led to health insurances (HI) bankruptcy in EU.

2. Problematics and objectives

High priced ATMPs started to reach the market while the governments are trying the cut health expenditures. ATMPs are expected to pose potential financial risks. Sovaldi® case highlights the limit of the current pricing policies which are unable to match affordability and drug prices. So far, there is no specific path for pricing and reimbursement of innovative novel therapies.

The aim of this thesis may be subdivided as follows:

- First, the aim was to identify the magnitude of ATMPs pipeline by assessing the number, status, and phase of development of ATMPs clinical trials, the type of ATMPs and the diseases targeted by the ATMPs, and to estimate the number and characteristics of discontinued ATMPs clinical trials in order to evaluate the trials discontinuation probability.
- The second objective was to evaluate the ATMPs expected budget impact in 3 different diseases: Alzheimer's disease (AD), Parkinson's disease (PD), and heart failure (HF), based on 5 assumptions of efficacy scenarios from the United Kingdom (UK) or French perspectives.
- Finally, the third objective was to identify, define, classify, compare the proposed approaches to fund innovative high-cost medicines published in the literature, to analyze their appropriateness for ATMPs funding and to suggest an optimal funding model for ATMPs.

3. General methodology

To accomplish these aims, the methodology was divided in 4 parts (Figure 3):

- In the introduction, an overview on ATMPs was presented: the definition of ATMPs, the types of ATMPs, the ATMP regulation in EU, the bodies responsible of ATMPs evaluation. In addition, we detailed the requirements for ATMPs in the pre-marketing authorization phase, the marketing authorization procedure and the post-marketing requirements. Then, the challenges facing the ATMPs were discussed: at R&D level, clinical development level and market access level.
- In chapter 1, the magnitude of ATMPs pipeline was evaluated through the assessment of the number of ATMP clinical trials in 3 different clinical trials databases: clinicaltrials.gov, International Clinical Trials Registry Platform (ICTRP) of the World Health Organisation (WHO), and the European Union Drug Regulating Authorities Clinical Trials (EudraCT). Trials were classified by type of ATMP, phase of development, number of enrolment, trial status, disease areas, and sponsor status. This study was completed by a review of a gene therapy clinical trial database.

  And in order to determine the probability that these products complete the development process and reach the market, we analyzed the probability of discontinuation of ATMPs clinical trials. To calculate this probability, the number

of withdrawn, terminated or prematurely ended ATMPs clinical trials was identified as well as the number of ongoing and completed ATMPs trials. Trial discontinuation probability was calculated for every category of ATMPs, in every phase and by sponsor status.

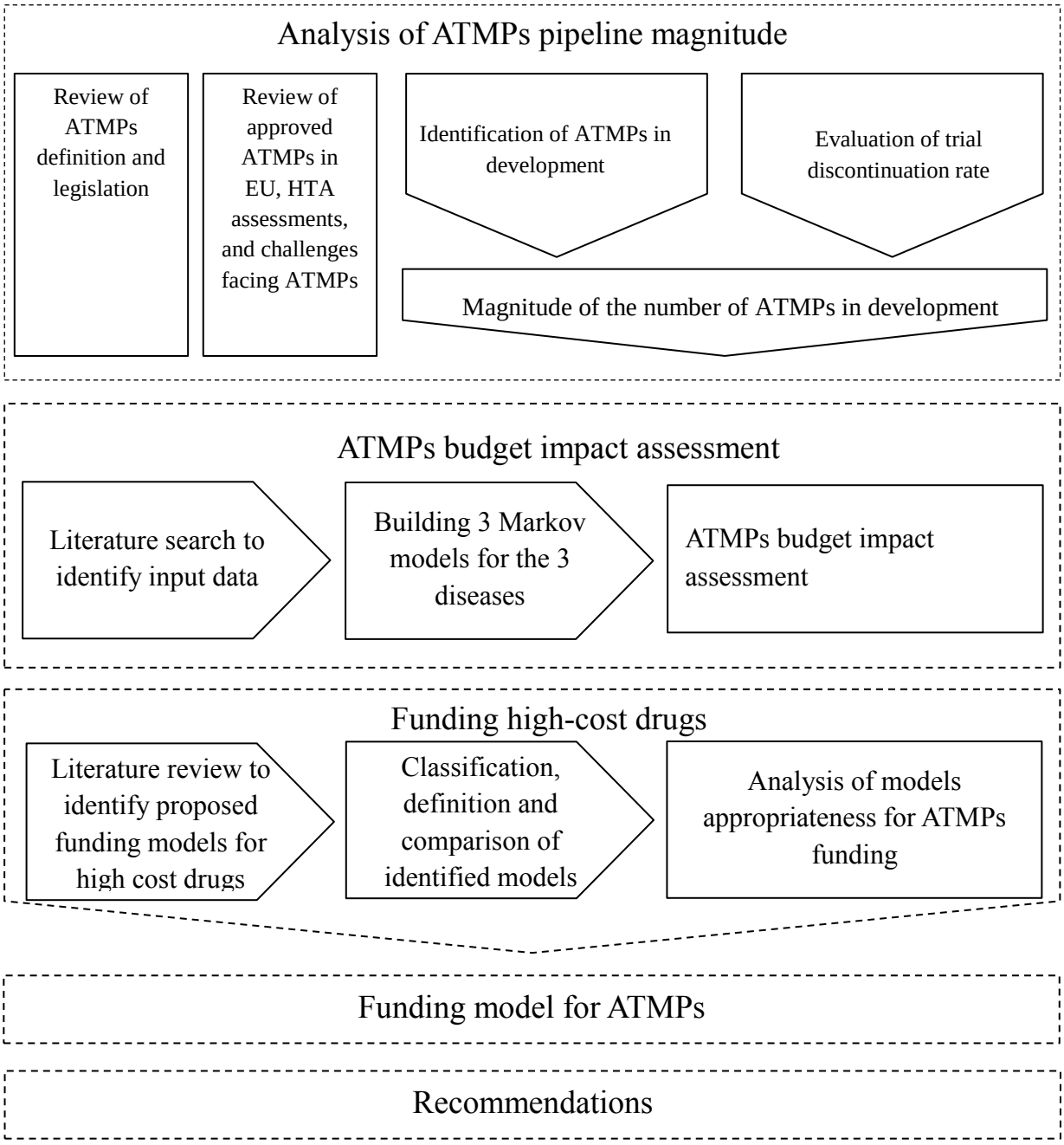
- In chapter 2, the ATMPs budget impact was assessed in 3 diseases: Parkinson's disease, Alzheimer's disease and heart failure, assuming 5 different efficacy scenarios. The UK payer and societal perspectives were adopted for PD and AD and the French payer perspective for HF.

  The considerations behind the choice of the diseases were the high medical unmet needs in these disease areas and the absence of curative therapies as well as the presence of ATMP in the pipeline in advanced stage of development targeting these diseases.

  Then, an evaluation of the budget impact of ATMPs in 35 diseases was conducted assuming an average fixed price for an ATMP in chronic disease and a higher price for ATMPs for orphan diseases.
- In the third chapter, a systematic literature review was conducted in Ovid Medline, Embase and the grey literature to identify studies on funding high cost drugs published between January 2010 and February 2017. Funding models were classified into groups and subgroups based on the nature of agreements. The definitions, advantages and limitations of each model were extracted. Then, an evaluation and comparison of the feasibility, acceptability, burden, financial interest, appeal for payers, and appeal for manufacturer was conducted. The appropriateness of each model to fund ATMPs was evaluated.

  An optimal sustainable funding model was recommended for ATMPs.
- Finally, health policy recommendations for the stakeholders – patients, physicians, payers and manufacturers – were presented. These recommendations aim to help decision-makers to ensure patient access to innovation while maintaining the sustainability of the healthcare system.

Figure 3. Overall study methodology



Chapter 1: Advanced Therapy Medicinal Products: Heterogeneous Class of Innovative Therapies

The major advances in the field of biotechnology, genetic engineering, toxicology, molecular biology and other related sciences (22) in the 21st century has led to a better understanding of pathophysiology and biochemical causes of diseases, and to the exploitation of biological components such as nucleic acid sequences, stem cells, for developing new advanced therapies. A new generation of biopharmaceuticals has emerged. A wide range of therapies are included in the area of biopharmaceuticals and the techniques used are divergent (23). Due to these new advanced therapies complexity, the European Parliament and the council of the European Union (EU) have put in place a regulation on the 13th of November 2007: Regulation (EC) No 1394/2007 (24) on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004. This regulation defines and regulates a class of biopharmaceuticals called: Advanced Therapy Medicinal Products (ATMPs).

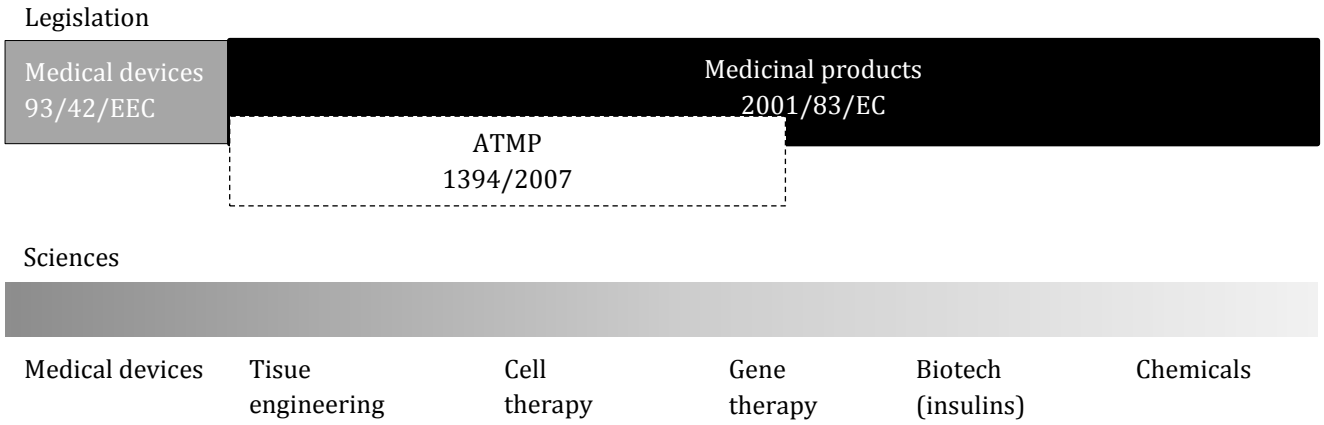
1. Advanced Therapy Medicinal Products Regulation

1.1. Introduction to Regulation (EC) No 1394/2007

Since 2001, all medicinal products, biological or chemical origin, have been regulated by the Directive 2001/83/EC (25). The ATMPs fall between medical devices and medicinal product. To cover this overlapping area, the EU parliament has implemented a new regulation in November 2007: Regulation (EC) No 1394/2007 (24), and started its application in December 2008. The aim of this regulation was *"ensure the free movement of these medicines within the European Union (EU), to facilitate their access to the EU market, and to foster the competitiveness of European pharmaceutical companies in the field, while guaranteeing the highest level of health protection for patients"* (26). The ATMP regulation created a single, harmonised framework for ATMPs that ensures universal standards of safety, quality and efficacy. It completed the legal framework for advanced therapies.

It applies to ATMPs over and above the requirements of the European regulatory framework set out in Directive 2001/83/EC (25). Standards for the human tissues and cell donation, procurement, testing, processing, storage and distribution are regulated under the Directive 2004/83/EC (27). Therefore, ATMP regulation was additional and complementary to the other regulations for medicinal products (Figure 4).

Figure 4. Advanced Therapy Medicinal Products legislation



*This figure was adapted from TERMIS PAP: Session 3 (28)

The 2 main elements in the new regulation were: a centralized Marketing Authorization (MA) procedure in Europe and a special committee in the European Medicines Agency (EMA) in charge of ATMP scientific assessment and classification: Committee for Advanced Therapies (CAT). In addition, it covers the supervision, and pharmacovigilance of ATMPs in Europe.

1.2. Advanced Therapy Medicinal Products definitions

According to the Article 2 of Regulation (EC) No 1394/2007 (24), in addition to the definitions laid down in Article 1 of Directive 2001/83/EC (25) and in Article 3, points (a) to (l) and (o) to (q) of Directive 2004/23/EC (27), ATMP is a class of biopharmaceuticals that encompasses:

- Gene Therapy Medicinal Product (GTMP)
- Somatic Cell Therapy Medicinal Product (sCTMP)
- Tissue Engineered Product (TEP)
- Combined Therapy Medicinal Product (CATP)

1.2.1. Gene Therapy Medicinal Product

As defined in Part IV of Annex I to Directive 2001/83/EC (25), gene therapy medicinal product is a biological product which has the following characteristics:

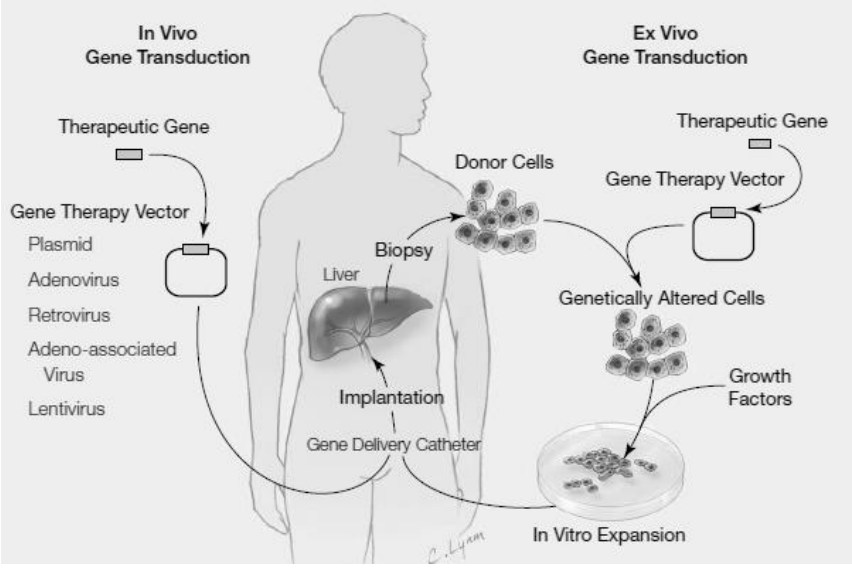
- *"contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;*

- *its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence."*

An important note to mention is that vaccines against infectious diseases are not considered as GTMP.

There are 2 approaches for gene therapies: the in-vivo and ex-vivo approaches. The in-vivo approach delivers the genetic material directly inside the human body using several vectors such as viral vector, non-viral vector and naked DNA. The ex-vivo approach consists of genetically modified somatic human cells; the cells are isolated from the human body, the gene is then transferred to the cells and the cells are reinjected to the body (Figure 5) (29).

Figure 5. In-vivo and ex-vivo approaches of gene therapy



The in-vivo approach on the left of the figure delivers the therapeutic gene directly to the patient using a gene therapy vector. The ex-vivo approach on the right delivers the therapeutic gene to cells extracted from the patient, and then the genetically modified cells are expanded and re-administered to the patient (Kaji EH, 2001 (29)).

1.2.2. Somatic Cell Therapy Medicinal Product and Tissue Engineered Product

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

- "*contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or*

structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor;

- *presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues."*

Somatic cells are all cells in the body except germline cells (sperm and egg).

Tissue Engineered product as defined in Article 2 of Regulation (EC) No 1394/2007(24):

- "*contains or consists of engineered cells or tissues,*
- *presented as having properties for, or is used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue*."

In order to be considered as "engineered" cell or tissue, the product has to fulfill at least one of these two following conditions:

- Substantial manipulation: biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved.
- Not intended to be used for the same essential function in the recipient as in the donor.

TEP may contain cells or tissues of human or animal origin, or both, viable or non-viable. Products containing exclusively non-viable tissues or cells and do not act principally by pharmacological, immunological or metabolic action, shall not be included in this class. In addition to cells and tissue, TEP may also contain bio-molecules, biomaterials, chemical substances.

The list of manipulation not considered as substantial manipulation as mentioned in Annex I of Regulation (EC) No 1394/2007(24):

— Cutting,

— Grinding,

— Shaping,

— Centrifugation,

— Soaking in antibiotic or antimicrobial solutions,

— Sterilization,

— Irradiation,

— Cell separation, concentration or purification,

— Filtering,

— Lyophilization,

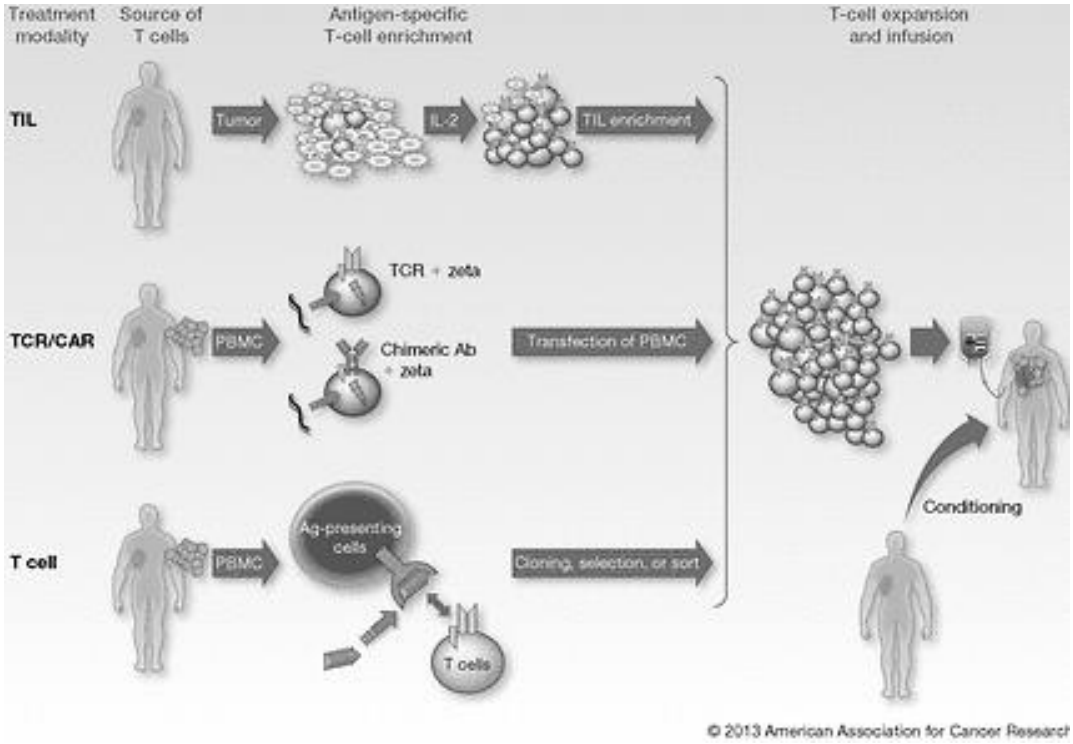
— Freezing,

— Cryopreservation,

— Vitrification

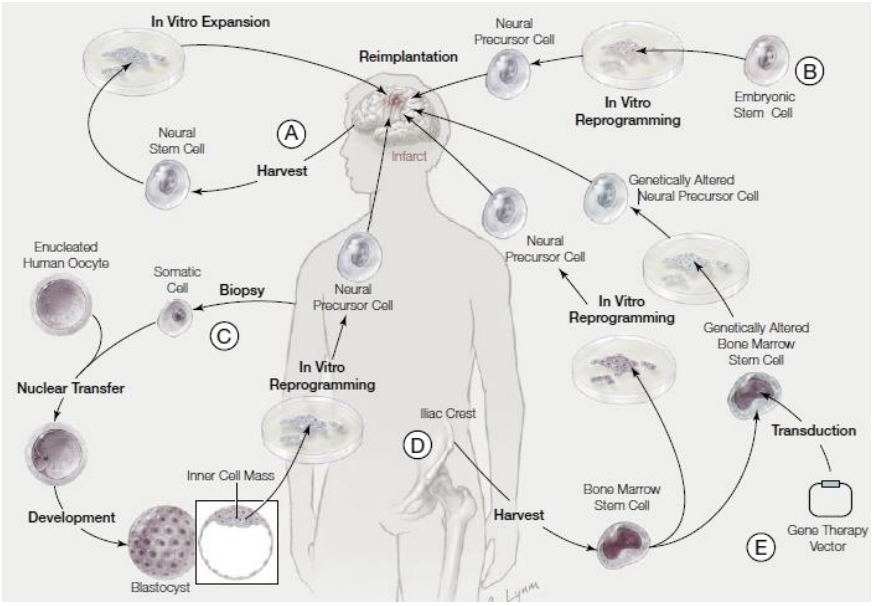
Figure 6 and Figure 7 show 2 examples of cell therapies: Figure 6 shows 3 different cell therapy modalities using tumor-infiltrating lymphocytes (TIL), gene-modified T cells engineered to express the desired T-cell receptor (TCR) or chimeric antigen receptor (CAR), and endogenous antigen-specific T cells (30) and Figure 7 shows cell therapies for cerebral infarction (29). Figure 8 shows an example of the procedure of cartilage repair using an autologous tissue engineered product (31).

Figure 6. Example of somatic therapy for cancer



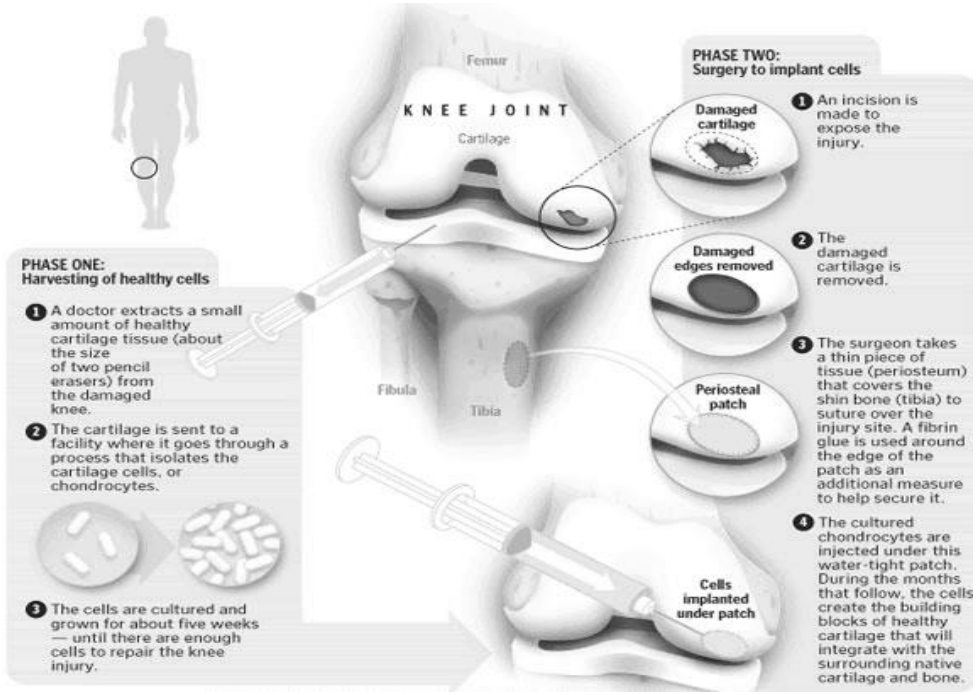
This figure shows the three general approaches for cancer therapy: (1) enrichment and expansion of tumor-infiltrating lymphocytes (TIL) from a disaggregated tumor biopsy sample using Interleukin 2 (IL2); (2) gene therapy: genetic transfer to Peripheral blood mononuclear cell (PBMC) of TCR-recognizing tumor antigen-derived peptide-MHC target or CAR-recognizing surface tumor protein; (3) enrichment of endogenous antigen-specific T cells from peripheral blood mononuclear cells (PBMC) by *in vitro* stimulation followed by cell selection or cloning (Yee C, 2013 (30)).

Figure 7. Possible approaches to stem cell therapy for cerebral infarction



A. neural stem cells are expanded in vitro and reimplanted in the brain to replace the lost neurons. B. human stem cells from allogeneic are reprogrammed in vitro into neural precursor cells implanted in the brain. C. somatic cells (e.g. skin cells) are obtained from patient and somatic nuclei are harvested and transferred to human oocyte. A blastocyst is formed then reprogrammed in vitro into neural precursor cell, implanted in the brain. D. bone marrow cells are harvested and reprogrammed in vitro into neural precursor, implanted in the brain. E. gene therapy: bone marrow stem cells are harvested genetically altered reprogrammed in vitro to become neural precursors and reimplanted in the brain (Kaji EH, (29)).

Figure 8. Example of tissue engineered product: autologous chondrocyte implementation procedure



The 2 phases of cartilage repair using the autologous cartilage implantation procedure are presented in this figure. The procedure starts by an extraction of healthy cartilage that will be cultured and expanded then a surgery is done to implant the cells and repair the injury (31).

1.2.3. Combined Therapy Medicinal Product

Combined advanced therapy medicinal product fulfills the following:

- *"it must incorporate, as an integral part of the product, one or more medical devices within the meaning of Article 1(2)(a) of Directive 93/42/EEC or one or more active implantable medical devices within the meaning of Article 1(2)(c) of Directive 90/385/EEC, and*
- *its cellular or tissue part must contain viable cells or tissues, or*
- *its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to."*

Classification by donor

Advanced Therapy Medicinal Product can be divided in 2 types: allogeneic and autologous.

- Autologous use is when tissue or cells are derived from the patient himself.
- Allogeneic cells and tissues are derived from a donor whose tissue type closely matches the patient's, the donor can be a family member or not (matched unrelated donor).

An advanced therapy medicinal product containing both autologous and allogeneic cells and tissues are considered as allogeneic use.

1.2.4. Borderline classification

The classifications of ATMPs, drugs and medical devices may be overlapping in some cases; therefore the classification may not be immediately obvious.

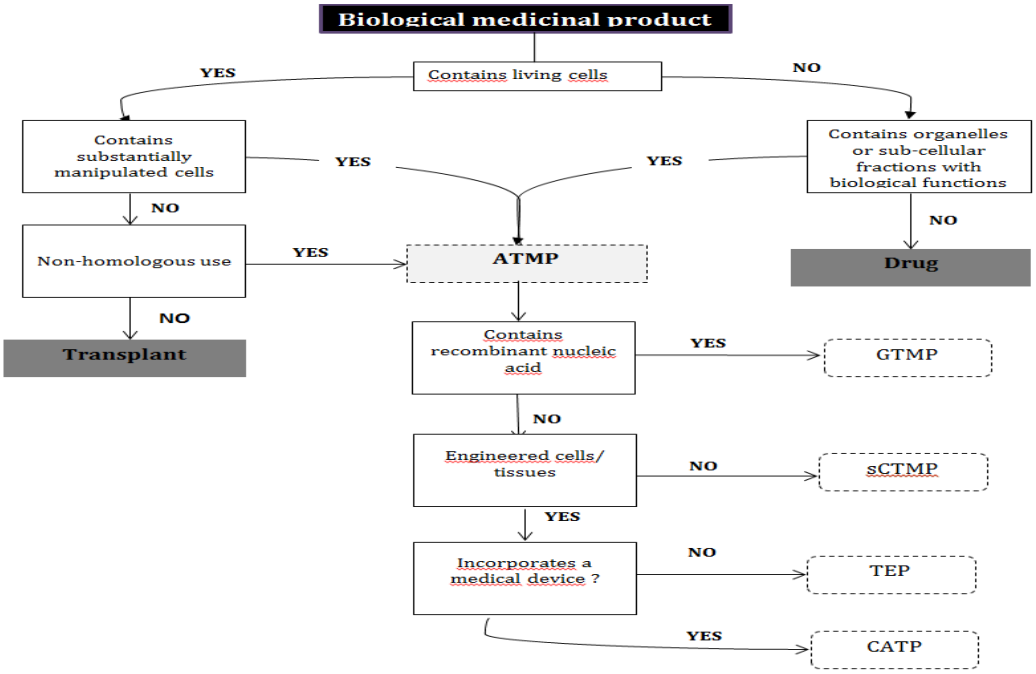
The regulation specifies that:

- If a product may fall under the categories of sCTMP and TEP, it has to be considered as TEP.
- If a product may fall under sCTMP or TEP and GTMP, it has to be considered GTMP.

Furthermore, there can be borderline cases with cosmetics, transplants or other product types.

Figure 9 presents a decision tree that helps to identify if a product should be classified as ATMP or not, and the ATMP class under which it falls.

Figure 9. Decision tree of ATMPs



GTMP: Gene Therapy Medicinal Product, sCTMP: Somatic Cell Therapy Medicinal Product, TEP: Tissue Engineered Product, CATP: Combined Therapy Medicinal Product.
This figure was adapted from Pacini S, 2014 (32)

1.3. Hospital Exemption (HE)

According to Article 28 of the Regulation (EC) No 1394/2007(24), some products are subject to hospital exemptions. Hospital Exemption is defined in the regulation as "*Advanced therapy medicinal products which are prepared on a non-routine basis according to specific quality standards, and used within the same Member State in a hospital under the exclusive professional responsibility of a medical practitioner, in order to comply with an individual medical prescription for a custom-made product for an individual patient, should be excluded from the scope of this Regulation whilst at the same time ensuring that relevant Community rules related to quality and safety are not undermined* ".

Tailor-made products on a non-routine basis constitute the hospital exemption and do not have to apply for a centralized MA. Member state has to authorize the ATMP manufacture under hospital exemption to ensure the quality of the products (33).

The hospital exemption provides an opportunity for ATMPs to demonstrate clinical proof-of-concept before undergoing formal clinical trials. In addition, it may constitute a

good opportunity for clinical academic centres developing ATMPs in early phase of development to benefit from this scheme.

1.4. Transitional period

1.4.1. Number of ATMPs before the regulation

The European Commission published in October 2012 a report with the Member States feedback on the number of ATMPs legally on the market, the number of ATMPs prepared on a routine basis, ATMPs that fall under HE and criteria applied for the latter ones (34). Twenty seven European countries replied to EC questionnaires, 10 countries had ATMPs legally on the market at that time 6 countries had ATMP with HE. Member States have reported 31 ATMPs legally on the EU market prior to the implementation of the ATMP Regulation. Same product may have been reported by more than one Member State. Table 1 summarizes some Member States responses (34).

Table 1. Number of ATMPs in the different Member States

Country	ATMPs legally on the market	Prepared on a routine basis	ATMPs falling under the hospital exemption	Criteria applied for hospital exemption
France	Chondrocelect®	Chondrocelect®	Preparing the decree about the national legal framework for the requirements of HE	The regulation criteria
Germany	-Chondrocelect® -transitional period: Hyalograft C®, CartiGro®, MACI® and CaReS®	Chondrocelect®	17 products which are legally on the market are all hospital exemptions.	Regulation criteria and an authorization of the product by the higher federal authority
Italy	3 ATMPs: Hyalograft C autograft (cartilage), Hyalograft 3D autograft e Laserskin autograft (skin)	-	-	Draft technical text is available
Spain	-Chondrocelect®	-	Corneal limbal stein cells, chondrocytes and skin keratinocytes.	Regulation criteria
United Kingdom	18 authorisations to manufacture and supply unlicensed ATMPs under the terms of the exemption provided by Article 5(1) of Directive 2001/83/EC	-	No products	Guidance for arrangements under the hospital exemption scheme
Sweden	Mesenchymal stem cells for Graft versus Host disease and a Chondrocyte	Chondrocyte implantation product	-	Manufacturers need to apply for a manufacturing licence

	implantation product			
Belgium	No ATMP	-	16 cell and tissue banks have been authorized to continue their activities	Further examination needed to identify the requirements

1.4.2. Transitional period timelines

A transitional period has been granted by the Article 29 of the Regulation (EC) N° 1394/2007 for ATMPs already on the market prior to the regulation in the different Member States. The transition period for gene and cell therapies was until 30 December 2011 and for tissue engineered products was until 30 December 2012. During this period, manufacturers have to comply with the ATMP regulation and submit a marketing authorization application for a centralized marketing authorization for their products (24, 35).

1.5. Committee for Advanced Therapies

The Committee for Advanced Therapies (CAT) is a committee within the EMA, established in accordance with Regulation (EC) No 1394/2007(24).

1.5.1. Members

According to Article 21 of Regulation (EC) No 1394/2007(24), CAT consists of:

- Five members or co-opted members of the Committee for Medicinal Products for Human Use (CHMP) from five Member States, with alternates. They are appointed by the CHMP;
- One member and one alternate appointed by each Member State not represented among the members and alternates of CHMP;
- Two members and two alternates appointed by the European Commission, in order to represent clinicians;
- Two members and two alternates appointed by the Commission, in order to represent patients' associations.

The committee chair is elected by serving CAT members from among its members. The CAT members and chair are appointed for a three-year renewable period. The list of CAT members and alternates names is published on EMA website, with their contact details; curriculum vitae; declaration of interests and confidentiality undertaking.

1.5.2. CAT tasks

CAT has the following tasks (24):

- Providing draft opinion on ATMP quality, safety and efficacy for final approval by the CHMP;
- Providing advice whether a product falls within the definition of an advanced therapy medicinal product;
- Providing advice on any question related to ATMP at the request of the Executive Director of the Agency or the Commission;
- Assisting scientifically in the elaboration of any documents related to the fulfilment of the objectives of the Regulation;
- Providing scientific expertise and advice for any Community initiative related to the development of innovative medicines and therapies which requires expertise in one of the scientific areas;
- Contributing to the scientific advice procedures.

1.6. Incentives of the ATMPs regulation

A number of incentives to manufacturers have been introduced by the Regulation (EC) No 1394/2007 in the Chapter 6 especially for small and medium-sized enterprises (SME). These incentives are

- Scientific advice on the design,
- Scientific advice fees reduction of 90% for SMEs and 65% for other applicants;
- Scientific recommendation on advanced therapy classification
- Certification of quality and non-clinical data: special to SMEs, these organizations can submit the available quality and non-clinical data for their ATMP to the CAT for scientific evaluation and certification. This evaluation applies the same scientific standards and technical requirements as during the assessment of MAA, just at an earlier stage of development. This helps SMEs to attract capital and to facilitate the ATMP's development through the clinical stage and marketing authorization.
- Reduction of the fees for marketing authorization by 50% for hospitals and SMEs if a public health interest in the ATMP can be proven; furthermore, 50%

fee reduction is also granted for post-authorization activities in the first year following the MA.

Manufacturers can also benefit from other incentives such as scientific advice or protocol assistance that are not special for ATMPs. These incentives will be detailed in the following sections.

1.7. CAT Scientific recommendation on advanced therapy classification

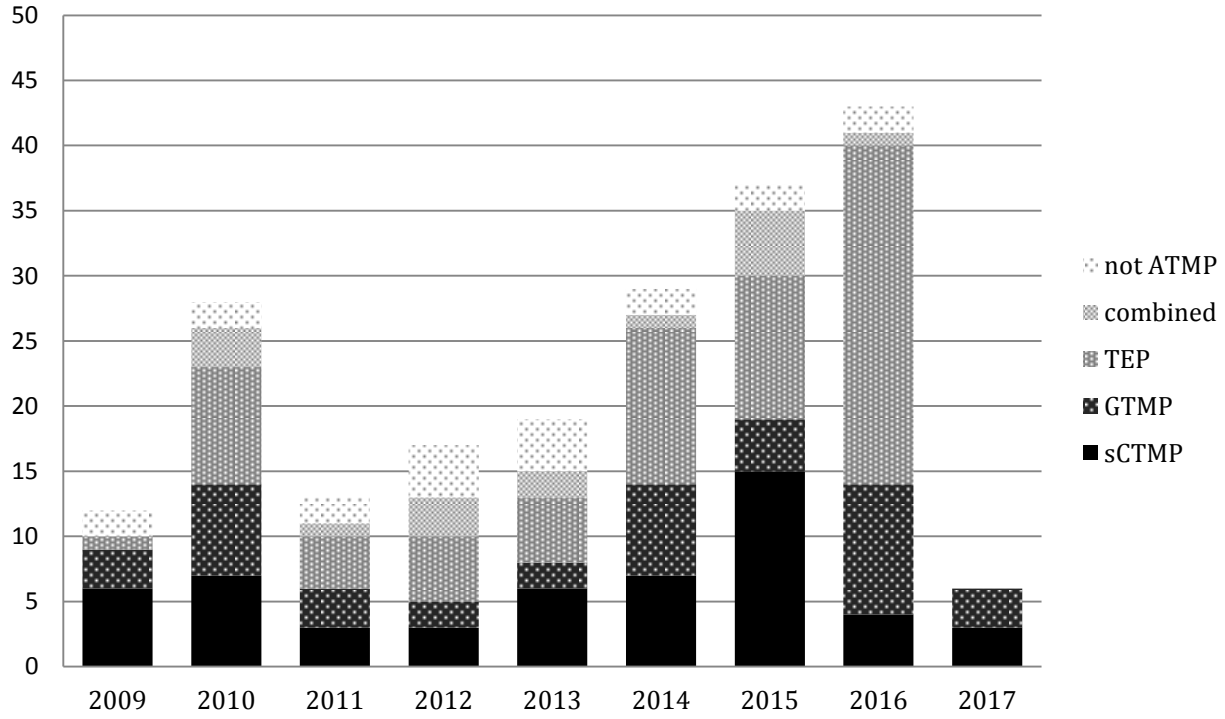
It is an optional free of charge procedure that allows ATMPs manufacturers to seek a scientific recommendation from CAT on whether their product can be classified as an ATMP. In some cases, the manufacturer is uncertain whether the product will fall under medicinal product, medical device or ATMP. Since the regulatory framework differs significantly between the various healthcare products, it is critical for manufacturers to have clarity about their products classification at an early stage of development.

After a 60-day procedure, the CAT issues a non-binding classification recommendation.

ATMP classification is done by the CAT according to the Article 17 of Regulation (EC) No 1394/2007. Summaries of scientific recommendations on classification of ATMPs are published on EMA website (36). Until May 2017, CAT has assessed 204 ATMP classification applications: 20 out of 204 (10%) were not considered an ATMP, 54 were classified as sCTMP, 41 GTMP, 73 TEP and 16 combined products.

Figure 10 shows the number of classifications per year by class of ATMPs. The number of ATMPs classification application has increased since 2009. In 2009, 12 products were assessed by CAT, 2 of them were classified not an ATMP and 6 sCTMP. The application number reached 28 in 2010 and then dropped to 13 applications in 2011. This number continued to grow to reach 43 applications in 2016; 2 out of 43 were not ATMP, 4 sCTMP, 10 GTMP, 26 TEP and 1 combined product.

Figure 10. Number of ATMP classified in each class by the CAT



GTMP: Gene Therapy Medicinal Product, sCTMP: Somatic Cell Therapy Medicinal Product, TEP: Tissue Engineered Product, CAT: Committee for Advanced Therapies
Data in this graph was extracted from EMA website (36).

2. Pre-marketing authorization

2.1. Risk-Based Approach

Risk factors is defined as "qualitative or quantitative characteristic that contributes to a specific risk following handling and/or administration of an ATMP" (37), they include:

- Nature and indication of the ATMP,
- Route of administration and dose,
- Cells origin,
- Phenotype stability,
- Initiation of immune response,
- Level of cell manipulation,
- Combination with biomolecules or structural biomaterials.

Risk-based approach is used to determine the nature and extent of the quality and (pre)clinical data to be included in the Marketing Authorization application (MAA). It is a flexible approach that is intended to evaluate and address the risk profile of each ATMP (Directive 2009/120/EC amending Directive 2001/83/EC). Long-term safety

issues such as infections, immunogenicity and device durability for combination ATMPs should also be considered. Furthermore, relevant safety endpoints need to be included in the clinical trials. The available safety, quality and efficacy data should enable a risk-benefit assessment by CAT.

The risk-based approach was introduced by the EU to create flexibility in the requirements for safety and efficacy of ATMPs (38). This approach aims to facilitate the science-driven development of ATMPs; it was used by manufacturers to justify deviations from the studies guidelines in 75% of the cases analyzed by Kooijman M. et al (38). The risk analysis can be used to inform the risk management plan (RMP) which needs to be part of a MAA.

The practical implementation of these legal requirements is outlined in the CAT Guideline on the risk-based approach according to Annex I, Part IV of Directive 2001/83/EC applied to Advance therapy medicinal products (Guideline on risk-based approach for ATMPs)(39). Requirements for pharmacovigilance are laid down in Directive 2001/20/EC, Regulation (EC) 726/2004 and 1394/2007 and the Good Clinical Practice (GCP) guidelines for ATMPs.

2.2. Manufacturing quality requirements

Manufacturing of biologics guidelines apply directly to ATMPs or can be a starting point for the ATMPs development. Good Manufacturing Practices (GMP) for ATMPs are being developed by EMA as amended in the Regulation 1394/2007. Indeed, in December 2016, EMA published the responses of the stakeholders on the ATMP GMP consultation draft.

For biological medicinal product (including ATMPs) the origin and history of starting raw materials needs to be described and documented.

The donation, procurement and testing of human tissues and cells is regulated on an EU-wide basis since 2004 (Directive 2004/23/EC). Procurement supervision systems are set up by Member States. Establishments for the donation or testing of cells or tissues need to be accredited, licensed or authorized.

2.3. Non-clinical data

Given the complexity of ATMPs a comprehensive non-clinical development program is needed. It is acknowledged that conventional pharmacology and toxicology studies may

be not appropriate for this type of products. Nevertheless, a certain number of non-clinical studies are required (Table 2).

Table 2. Non-clinical studies required for ATMPs

Non-clinical studies for gene therapies	Non-clinical studies for cell therapy and tissue engineering
• Proof of concept • Bio-distribution • Toxicity assessment • Immunogenicity • Carcinogenicity • Vector expression • Insertional mutagenesis germline transmission • Environmental risk assessment GMOs	• Proof of concept • Bio-distribution • Toxicity assessment • Immunogenicity • Tumourgenicity • Integration of the product • Functional integration • Paracrine effects • Cell differentiation • Gonads assessment

2.4. Clinical data

ATMPs clinical trials need to adhere to international ethical and quality standards known as Good Clinical Practice (GCP) guidelines. In addition, a detailed GCP special for ATMPs was drawn up by the EC in 2009 to address the special nature of ATMPs.

2.4.1. Studies to be included in clinical dossier – GTMP

- Pharmacokinetic studies: Shedding studies (dissemination of vector/virus through secretions and/or excreta), Dissemination studies – cell tropism, route of administration, target organ/cells, vector type and indication, as well as clinical feasibility and ethical acceptability.
- Pharmacodynamics studies
- Dose selection and schedule
- Immunogenicity
- Clinical efficacy
- Clinical safety
- Pharmacovigilance and risk management plan: Gene therapy medicinal products need adequate designed long-term studies to monitor specific efficacy and safety issues (40).

2.4.2. Studies to be included in clinical dossier – sCTMP

For sCTMP, the clinical development program should fulfil the same requirements like other medicinal products. The clinical development plan should include pharmacodynamic studies, pharmacokinetic studies, mechanism of action studies, dose finding studies and randomised clinical trials in accordance to the Directive 2001/20/EC and to the existing general guidances and specific guidances for the condition evaluated (41).

3. Marketing authorization

3.1. ATMPs guidelines

Several scientific guidelines were developed by EMA to help pharmaceutical industries to prepare the marketing authorization application for ATMPs. Below is a list of ATMPs guidelines available on EMA website and in the European Pharmacopoeia database (42):

- The overarching guideline for human gene therapy medicinal products is the Note for guidance on the quality, non-clinical and clinical aspects of gene transfer medicinal products (CHMP/GTWP/671639/2008),
- Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products (CHMP/GTWP/125491/06),
- Reflection paper on design modifications of gene therapy medicinal products during development(EMA/CAT/GTWP/44236/2009),
- Reflection paper on quality, non-clinical and clinical issues relating specifically to recombinant adeno-associated viral vectors (CHMP/GTWP/587488/07),
- ICH Considerations - Oncolytic Viruses(EMEA/CHMP/ICH/607698/2008),
- Guideline on quality, non-clinical and clinical aspects of medicinal products containing genetically modified cells(CAT/CHMP/GTWP/671639/2008),
- Guideline on the non-clinical studies required before first clinical use of gene therapy medicinal products (EMEA/CHMP/GTWP/125459/2006),
- Guideline on non-clinical testing for inadvertent germline transmission of the gene transfer vectors (EMEA/273974/2005),
- Reflection paper on management of clinical risks deriving from insertional mutagenesis (CAT/190186/2012),
- Guideline on follow-up of patients administered with gene therapy medicinal products (EMEA/CHMP/GTWP/60436/2007),

- The overarching guideline for human cell- based medicinal products is the guideline on human cell-based medicinal products (EMEA/CHMP/410869/2006),
- Reflection paper on stem cell-based medicinal products (EMA/CAT/571134/2009),
- Reflection paper on in-vitro cultured chondrocyte containing products for cartilage repair of the knee (EMA/CAT/CPWP/568181/2009),
- Guideline on xenogeneic cell-based medicinal products (EMEA/CHMP/CPWP/83508/2009),
- Guideline on potency testing of cell based immunotherapy medicinal products for the treatment of cancer (CHMP/BWP/271475/06),
- Reflection paper on clinical aspects related to tissue engineered products (EMA/CAT/573420/2009).

3.2. Marketing authorization application

The marketing authorization application (MAA) for ATMPs is similar to any medicinal product MAA with technical adaptations. Submission of applications to EMA involves:

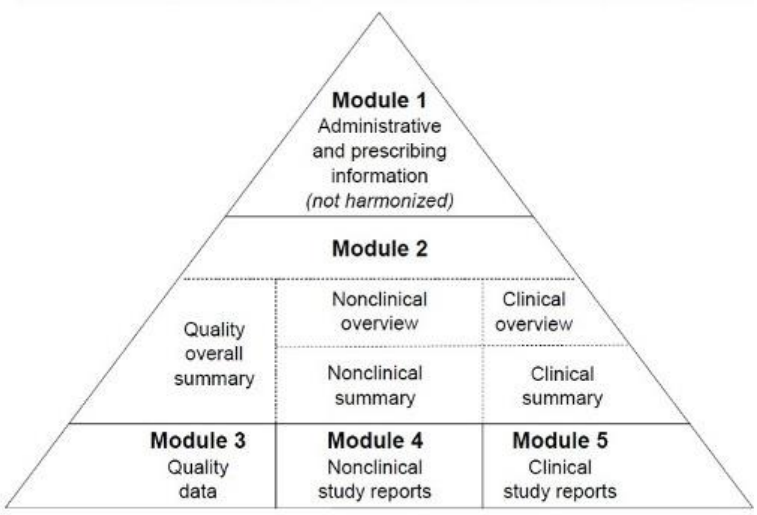
- Members of the Committee for Medicinal Products for Human use (CHMP)
- Committee for Advanced Therapies (CAT)
- Pharmacovigilance Risk Assessment Committee (PRAC)

The full application should be submitted with a dossier including the following information:

- Pharmaceutical (physico-chemical, biological or microbiological) tests
- Preclinical (toxicological and pharmacological) tests
- Clinical trials
- Any relevant published literature should also be included

A Common Technical Document (eCTD) is submitted, it must have the structure presented in Figure 11 .

Figure 11. Common Technical Document structure



Environmental risk assessment

MAA of an ATMP like other medicinal products needs to include an environmental risk assessment (ERA). General guidance for medicinal products for human use is provided (2006). A specific guidance was issued for GTMPs (37).

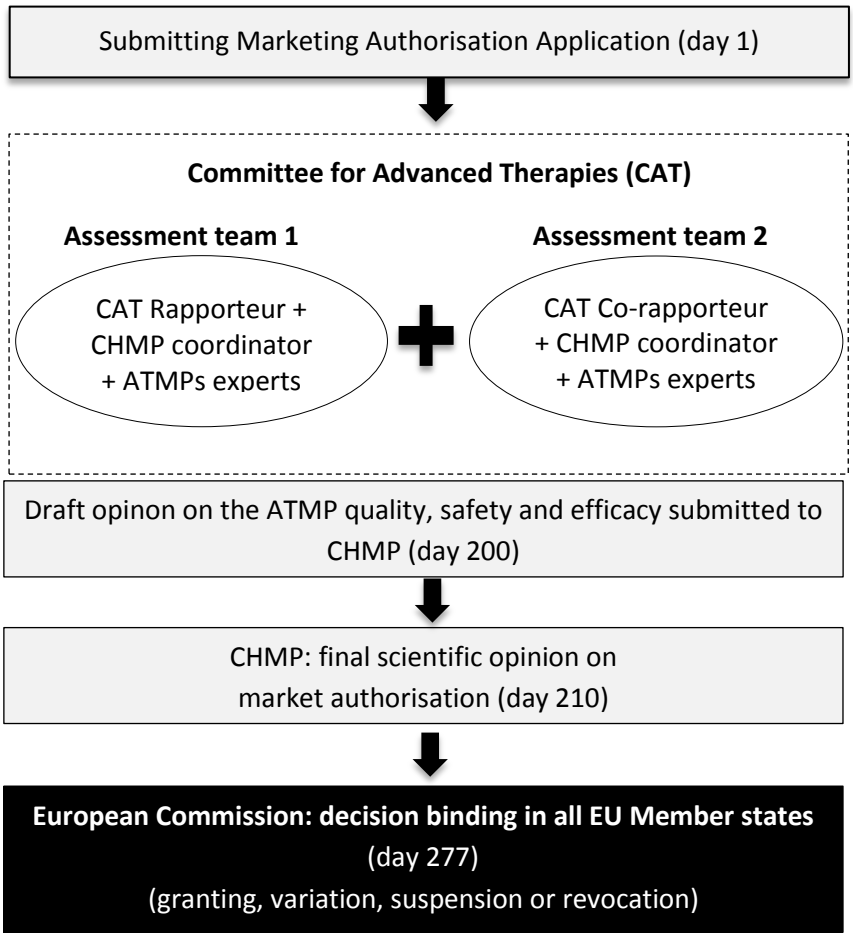
3.3. Centralized marketing authorization procedure

Article 8 of Regulation (EC) No 1394/2007(24), describes the ATMP evaluation procedure (Figure 12):

- CHMP consults the CAT on any scientific assessment needed to have the scientific opinions referred to in Article 5(2) and (3) of Regulation (EC) No 726/2004. CAT can also be consulted during re-examinations.
- When preparing a draft opinion for final approval by CHMP, the CAT shall endeavour to reach a scientific consensus. If such consensus cannot be reached, the Committee for Advanced Therapies shall adopt the position of the majority of its members.
- The CAT draft opinion shall be sent to the Chairman of the CHMP.
- The CHMP scientific opinion on ATMP may be not in accordance with the draft opinion of the Committee for Advanced Therapies. In this case, CHMP shall annex to its opinion a detailed explanation of the scientific grounds for the differences.
- The Pharmacovigilance Risk Assessment Committee ("PRAC") provides recommendations to the CHMP on pharmacovigilance matters.

- The Paediatric Committee ("PDCO") intervenes on aspects related with the obligations imposed under Regulation (EC) No 1901/2006 of the European Parliament and of the Council.
- The Committee on Orphan Medicinal Products ("COMP") provides scientific opinions to the Commission on aspects related to the application of the orphan incentives (this committee is only involved therefore if the applicant seeks orphan status).

Figure 12. Marketing authorization procedure



CAT: Committee for Advanced Therapies; CHMP: Committee for Human Medicinal Products; ATMP: advanced therapy medicinal product; EU: European Union.

3.4. Marketing authorization timelines

The procedure starts after the application validation by EMA and when all CAT (Co)-Rapporteurs and CHMP Coordinators have received the dossier and all additional information requested during validation.

Table 3 shows the standard timetable for the evaluation of an Advanced Therapy Medicinal Product (ATMP) under the centralized application (43).

Table 3. Standard timetable for the evaluation of an Advanced Therapy Medicinal Product (ATMP)

Day	Action	Responsibilities
1	Start of the procedure	
80	CAT (co)-rapporteurs assessment report(s) sent to CHMP Coordinators, CAT and CHMP members and the EMA. EMA responds to the applicant with preliminary conclusions that do not represent the position of CAT/CHMP	CAT (co)-rapporteurs
100	Comments from CHMP Coordinators, members of the CAT and the CHMP (including peer reviews)	CHMP Coordinators, members of the CAT and the CHMP
115	Draft list of questions from CAT (co)-rapporteur, as discussed with the CHMP Coordinators, peer reviewers, CAT and CHMP members and the EMA	CAT (co)-rapporteurs
120	CAT adoption of the list of questions, overall conclusions, and review of the scientific data to be sent to the applicant by the EMA	CAT
120	GMP/GLP/GCP Inspection procedure starts [Clock stop]	CAT
121	Submission of the responses including revised SPC, labelling and package leaflet texts in English [restart of the clock]	Applicant
150	Joint response assessment report from CAT (co)-rapporteurs received by CHMP coordinators, CAT and CHMP members and the EMA EMA respond to the applicant with preliminary conclusions that do not represent the position of CAT/CHMP	CAT (co)-rapporteurs
160	Deadline for comments from CAT and CHMP members to be sent to CAT (co)-rapporteurs, CHMP coordinators, EMA and other CAT and CHMP members	CAT and CHMP members
170	CAT discussion and decision on the need for adoption of a list of outstanding issues and/or oral explananation by the applicant (* if oral explanation is needed, the clock is stopped to allow the applicant to prepare the oral explanation)	CAT
171	CAT oral explanation Discussion on the draft opinion and identification of the recommendations for MA/refusal which will be transmitted to CHMP Final draft of English SPC, labelling/package leaflet + where needed an updated RMA plan and traceability system	CAT
180	CHMP disscusion on the Grounds for approval/refusal as adopted by CAT	CHMP
200	Draft opinion and draft Assessment Report transmission to the CHMP	CAT
210	Adoption of CHMP Opinion and CHMP Assessment Report	CHMP

CAT: Committee of Advanced Therapies, CHMP: Committee for Medicinal Products for Human Use

After adoption of a CHMP opinion, applicant is requested to provide the following annexes to EMA:

- Summary of product characteristics
- Final translations of summary of product characteristics, labeling and package leaflet in the 20 languages

The European commission makes the final decision.

3.5. Marketing authorization fees

The fee for marketing authorization shall be reduced by 50% if the applicant is a hospital or a micro, small and medium-sized enterprise (SME) and able to prove the interest of the ATMP concerned. This also accounts for fees charged by the Agency for post-authorization activities in the first year following the granting of the marketing authorization for the ATMP (24). The general marketing authorization fees paid for EMA are summarized in Table 4 (44).

Table 4. Payable fees

Full marketing authorization		Fees
Basic	Single strength associated with one pharmaceutical form and one presentation (basic fee)	278,800€
Additional	For each additional strength or pharmaceutical form including one presentation, submitted at the same time as the initial application for authorisation (additional fee)	+ 28,000€
Additional	For each additional presentation of the same strength and pharmaceutical form, submitted at the same time as the initial application for authorisation (additional fee)	+7,000€

The strength is defined as follows (45):

• *"For single-dose preparations, total use, the strength is defined as the amount of active substance per unit dose*

• *For multi-dose preparations, the strength is defined as the concentration expressed as the amount of active substance per ml, per puff, per drop, per kg, per m^2, as appropriate."*

3.6. Regulatory Early access tools & Development support

Regulation (EC) No 726/2004 (46) includes a number of provisions and early access tools aiming to foster patients' access to new medicines that fulfill important unmet clinical needs (47). In view of the promising clinical potential of ATMPs, ATMPs can also benefit from those tools.

3.6.1. Accelerated assessment

This procedure is applicable for therapies of major interest in particular innovation; it reduces the marketing authorization application assessment to 150 days instead of 210 days. Submit request with the claim that the medicinal product addresses to a significant extent the unmet medical needs have to be submitted 2-3 months before MAA submission.

3.6.2. Conditional MA

This procedure applies for medicinal products for seriously debilitating diseases or life-threatening diseases, emergency situations and orphan drugs. The product has to prove a positive risk-benefit balance, fulfilment of unmet medical need. It consists of an earlier authorization on the basis of incomplete clinical data. Manufacturers provide complementary data in a timeframe after authorization. It is requested at submission of MAA.

3.6.3. CHMP Compassionate use opinion

Unauthorized medicinal products indicated for chronically debilitating or life-threatening diseases for a group of patients with no alternative treatments. A member state (MS) can decide to make the medicinal product available for compassionate use, available to patients through national patients' access programs (prior to a marketing authorization).The Competent Authority of a MS must notify the EMA.

3.6.4. Development support: PRIME

The PRIME was launched by EMA to ensure rapid market access to promising medicines where a major public health interest presents significant unmet medical need. It is applicable for therapies of major interest in particular innovation. PRIME is a voluntary scheme that aims to optimize the generation of robust clinical data and accelerate authorization application assessments. It helps to:

- Accelerated assessment potential identification,
- Early rapporteur appointment,
- Reinforced scientific and regulatory support from the SAWP/ CHMP, other relevant scientific committees and EMA,
- Dedicated contact person within EMA.

The manufacturer applies to this procedure during development after having preliminary clinical evidence and identification of the unmet medical need and its magnitude. To date, eight ATMPs have been granted PRIME designation evidencing its value (Table 5).

Table 5. ATMPs accepted in PRIME scheme

Drug	Indication	PRIME date
KTE-C19 CAR-T	Diffuse Large B-Cell Lymphoma	01/06/2016
BMN270 gene therapy	Haemophilia A	01/02/2017
AMT-060 gene therapy	Haemophilia B	25/04/2017
SPK-9001 gene therapy	Haemophilia B	02/03/2017
LentiGlobin gene therapy	β-thalassemia	21/09/2016
AVXS-101 gene therapy	Spinal muscular atrophy type 1	31/01/2017
SPEAR TCR therapy	Synovial sarcoma	28/07/2016
JCAR017 CAR-T	Diffuse Large B-Cell Lymphoma	20/12/2016

3.6.5. Innovation Task Force (ITF)

It is an early dialogue between applicants and a multidisciplinary group (scientific, regulatory and legal competences) to proactively identify issues related to emerging innovative therapies and technologies. It helps to prepare for regulatory processes. Applicants are mainly SME and academics. This dialogue is free of charge (48).

3.6.6. Micro-, Small- and Medium-sized-Enterprise (SME) Office

The Micro-, Small- and Medium-sized-Enterprise (SME) are defined as follows (Commission Recommendation 2003/361/EC) (49):

- Micro enterprise: Annual work unit (AWU)< 10, Annual turnover ≤ €2M Or Annual balance sheet total ≤ €2M.
- Small enterprise: Annual work unit (AWU)< 50, Annual turnover ≤ €10M Or Annual balance sheet total ≤ €10M.
- Medium enterprise: Annual work unit (AWU)< 250, Annual turnover ≤ €50M Or Annual balance sheet total ≤ €43M.

EMA offers incentives for SME. Within the EMA, a dedicated personnel is present to provide administrative and procedural assistance, monitor MAA and organise training sessions for SMEs.

3.6.7. Scientific advice and protocol assistance

Scientific advice: EMA provides advices on the development and trials of a medicine in response to the company questions. A 90% reduction for SMEs and a 65% reduction for other applicants shall apply for such scientific advice or for advice on the conduct on the tests and trials necessary to demonstrate the quality, safety and efficacy of the ATMPs.

Manufacturer may request advice on the design and conduct of the pharmacovigilance and of the risk management system.

Parallel scientific advice with Health Technology assessment (HTA) bodies: helps to gain feedback from regulators and HTA bodies simultaneously, on the evidence that both parties request to determine a medicine's benefit-risk balance and value.

Table 6. Summary of financial incentives for ATMP developers and/or SME

	Fee reduction	
Type of fee	ATMP developer	SME
Certification procedure for SME	**↓90%**	N/A
Any scientific advice	**↓65%**	**↓90%** (**↓100%** for designed orphan drug)
Inspection (pre-authorisation)	-	**↓90%**, Deferral of total applicable fee*
Application for marketing authorisation	**↓50%** (if applicant is a hospital)	Deferral of total applicable fee* Conditional fee exemption, where EMA scientific advice is followed and MA application is not successful

* Up to 45 days after the date of the notification of the final decision on the marketing authorisation or of the withdrawal of the application.

4. Post-authorisation requirements

Article 14 of Regulation (EC) No 1394/2007 required the MA holder to submit in the MA application "*the measures envisaged to ensure the follow-up of efficacy of advanced therapy medicinal products and of adverse reactions thereto*." In this same article, EMA was requested to prepare guidelines for the post-authorization follow-up of efficacy and adverse reactions, and risk management. EMA has issued a detailed guideline on this matter (Guideline on Safety and Efficacy Follow-up - Risk Management of ATMPs 2008) (50). ATMPs need to comply with post-marketing requirements like other medicinal

products; safety and effectiveness data are continuously collected, evaluated and reported, to allow a benefit-risk management.

The risk management is "*a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those interventions*" (EMEA/CHMP/96268/2005). Risk management is a cycle that starts by risk identification from clinical trials, literature review and epidemiological studies, followed by risk characterization and assessment, then risk minimization and effectiveness measurement (51) . The safety and efficacy follow-up systems should be part of the risk management plan.

There are specific rules for ATMPs with unique safety & efficacy concerns, as well as consideration of endpoints that MA holders need to comply with when designing post-authorization follow-up studies. The guideline on safety and efficacy follow-up-risk management of advanced therapy medicinal products (52) detailed all additional requirements for the Risk Management Plan (RMP) for market authorisation holders of approved ATMPs: Safety specifications, Pharmacovigilance plan, Evaluation of the need for efficacy follow-up, Risk Minimization plan, and Efficacy follow-up plan.

5. Approved ATMPs in EU

Ten years after the regulation implementation, nine ATMPs have been granted a marketing authorization in the EU. Approved ATMPs are targeting different diseases and conditions.

5.1. Chondrocelect®

In October 2009, Chondrocelect® was the first approved ATMP in EU, it is a tissue engineered product. It is a suspension for implantation that contains characterised viable autologous cartilage cells expanded ex vivo expressing specific marker proteins. It is used in adults with single cartilage defect in the femoral condyle, it repairs damage to the cartilage in the knee (53).

5.2. Glybera®

Glybera®, Alipogene tiparvovec, was approved in October 2012, it is a gene therapy medicinal product indicated for the treatment of lipoprotein lipase deficiency (54).

Glybera® was designated as an orphan drug EU/3/04/194 on 8 March 2004. It was approved under "exceptional circumstances". The exceptional circumstances mean that the applicant showed that they were unable to provide comprehensive data on the efficacy and safety of the medicine due to the rarity of the condition, limited scientific knowledge in the area concerned, or ethical considerations involved in the collection of clinical data. It is under additional monitoring.

5.3. MACI®

MACI® is a tissue engineered product approved in June 2013 for the treatment of cartilage defects. It consists of matrix applied characterized autologous cultured chondrocytes (55).

5.4. Provenge®

Provenge®, Sipuleucel-T, was the first somatic cell therapy product approved in September 2013. It contains autologous peripheral blood mononuclear cells activated with PAP-GM-CSF (sipuleucel-T). Provenge® is an immunotherapy indicated for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer (mCRPC) adults in whom chemotherapy is not yet clinically indicated (56). It is under additional monitoring. This means that it is being monitored even more intensively than other medicines.

5.5. Holoclar®

Holoclar®, ex-vivo expanded autologous human corneal epithelial cells containing stem cells, was approved in February 2015 in EU. It is a tissue engineered product, used in the eye to replace damaged cells on surface (epithelium) of the cornea. It is used in adult patients with moderate to severe limbal stem-cell deficiency caused by burns, including chemical burns, to the eyes (57). It was granted an orphan designation (EU/3/08/579) on 7 November 2008. It is under additional monitoring. Holoclar® has a conditional approval which means that the committee positive opinion was based on data which, while not yet comprehensive, indicate that the medicine's benefits outweigh its risks. Further studies are requested, the approval is renewed on a yearly basis until all obligations fulfilment after which the normal approval is issued.

5.6. Imlygic®

Imlygic®, talimogene laherparepvec, a gene therapy approved in December 2015, it is a cancer medicine used to treat adults with unresectable melanoma that is regionally or distantly metastatic (Stage IIIB, IIIC and IVM1a) with no bone, brain, lung or other visceral disease (58). It is under additional monitoring.

5.7. Strimvelis®

It is a gene therapy approved in 2016, indicated for the treatment of patients with severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), for whom no suitable human leukocyte antigen (HLA) - matched related stem cell donor is available. It consists of autologous CD34+ enriched cell fraction that contains CD34+ cells transduced with retroviral vector that encodes for the human ADA cDNA sequence (59). Strimvelis® was designated as an orphan medicinal product on 26 August 2005. It is under additional monitoring.

5.8. Zalmoxis®

It is a somatic cell therapy product approved in 2016, indicated as adjunctive treatment in haploidentical haematopoietic stem cell transplantation (HSCT) of adult patients with high-risk haematological malignancies. It consists of allogeneic T cells genetically modified with a retroviral vector encoding for a truncated form of the human low affinity nerve growth factor receptor (ΔLNGFR) and the herpes simplex I virus thymidine kinase (HSV-TK Mut2) (60). It was designated an orphan medicinal product on 17 September 2003. Zalmoxis® has a conditional approval and it is under additional monitoring.

5.9. Spherox®

Spherox® is an autologous medicinal product that contains spheroids of human autologous matrix-associated chondrocytes. It is a TEP, administered by intraarticular implantation for adults to repair the symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) with defect sizes up to 10 cm2. It was granted a marketing authorization on 10 July 2017 (61).

6. Challenges facing ATMPs

Several challenges are facing ATMPs manufacturers at research & development (R&D) and manufacturing level, clinical level and then at market access and commercialization level.

6.1. Research & Development (R&D) and manufacturing challenges

6.1.1. ATMP complexity

ATMPs are personalized therapies; the preparation of an ATMP may consist of extracting cells from the patient himself or from another donor. Cells are complex and labile active substances that can react to the micro-environment they are exposed to. Some specific features need to be addressed in case of cell or tissue therapies: cell heterogeneity, stability, identity, purity, viability, potency, persistence, sterility and potential tumourgenicity.

With combined ATMPs, a particular emphasis should also be given to matrix biodegradation aspects and matrix-cell interactions.

In addition, cells are very sensitive with short shelf lives, manufacturing may be a complicated process, for example (62):

- Holoclar®: biopsies taken from the patient need to be sent to the manufacturer in 24 hours, its shelf life is 36 hours.
- Provenge® shelf life is 18 hours in a cooled insulated container.

ATMPs are complex products and risks may differ between products, depending on the materials used and complexity of the manufacturing process. Produced ATMPs may entail some variability due to the use of biological materials and complex manipulation steps (e.g. cells cultivation, substantial manipulations, etc.). In addition, the manufacture and testing of ATMPs pose specific challenges and the strategies implemented to ensure a high level of quality must be tailored to the constraints of the manufacturing process, limited batch sizes and the inherent variability of the starting material.

There is a lack of clear quality standards for ATMPs production. Good Manufacturing Practices (GMP) guidelines for ATMPs are being developed by the European Commission. A Consultation Document has been published in June 2016 to collect relevant evidence and information from stakeholders on this topic (63).

6.1.2. Safety considerations

According to the Regulation (EC) No 1394/2007, ATMPs are regulated more like pharmaceuticals than like medical devices. Some safety and quality requirements for biological materials, excipients, and reagents can be difficult to meet (64). Human cells and tissues for human application must be donated, procured and tested in accordance with the EU Directives on quality and safety (65-67).

The use of ATMPs may be associated with specific risks to the patients. These risks are determined by various risk factors, which are related to the biological activity, quality, and application of the ATMP. In February 2013, EMA published the "Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products" to address and evaluate potential risks (39).

Risks associated to virus/vectors used for gene therapies

- Replication recombinant viruses (RCV): ability of a viral vector to spontaneously become self-replicating and potentially pathogenic (68).
- Potential risk of germline alteration and reactivation of latent viruses

Risks associated with sCTMP and TEP (69):

- Tumorigenic potential of cell-based products must be investigated, the cells proliferative capacity and point of senescence should be determined.
- TEPs tumorigenicity testing includes testing of the final construct, in a suitable animal model that reflects the site of administration as far as possible.
- Distribution of the cells following administration should be identified and supported by the risk analysis, end-organ accumulation, ectopic grafting and unintended in vivo transformation.
- For combined ATMPs, the device element of the combination should be included in the safety studies. A CE –mark is not sufficient for the device because this is given in the context of the intended use specified by the device manufacturer.
- Viable allogeneic cells give rise to specific challenges: the prediction of the human immune response. Autologous cells or tissues may be helpful to avoid xenogeneic response

6.2. Clinical development: Evidence generation challenges and ethical dilemmas

The clinical development requirements applied to ATMPs are the same as for medicinal products. Pharmacokinetics, mechanism of action studies and randomised clinical trials should be performed in accordance to Directive 2001/20/EC. However, studies to define the clinical target dose may not be applicable and require alternative approaches to establish at least a minimally effective dose. And due to the biological characteristics of cell-based products, alternative approaches to Phase 1 to Phase 3 trials may be required. Furthermore, appropriate comparator therapies or products may not always be available.

In case of human tissue or cells based products, donor requirements such as the consent, eligibility of donors, compensation, data protection and confidentiality, selection, evaluation and procurement, outlined in the European Union Tissue and Cells Directive (EUTCD) should be met. In addition, the Good Clinical Practice (GCP) requirements for accountability of investigational medicinal products need to be incorporated.

The evidence generation concerns for ATMPs are similar to those for cancer treatments and orphan drugs. Conducting randomized clinical trials may be difficult for several reasons; the small population and the serious progressive symptoms that characterize several chronic diseases make the generation of robust clinical evidence very difficult because of ethical and practical barriers. The recruitment into adequate sample sized would require multiple centers and may be very expensive. Single-arm trials or small Randomized clinical trials are likely to be the common study designs. Glybera® was approved following two clinical trials of only 19 subjects (70). In addition, the trials are likely to report the use of primary surrogate endpoints. Surrogate endpoints have generally implications on increasing the uncertainty during regulatory assessment. It should be explicitly justified via a systematic review and the relationship between surrogate and final outcome need to be validated (71).

A consultation with regulatory authorities such as CAT is recommended to establish the clinical development programme. Early dialogue with payers and regulators is necessary to ensure robust and acceptable data from clinical trials. Furthermore, in cases of diseases with no alternative treatments, it may be considered unethical to withhold experimental treatment from participants.

In addition, the absence of long-term data at the time of launch generates uncertainties that will complicate the challenge of the evaluation of ATMP value by payers. Clinical efficacy or safety might only be apparent after several years. In case of combined ATMPs, the durability of the medical device and its influence on the cells must also be addressed. Follow-up of efficacy and adverse events reporting are crucial.

Uncertainty is a main concern in case of ATMPs like for regenerative medicines. In the National Health Services report by Hettle R et al, 2017, it was concluded that regenerative therapies will be associated with a significant level of uncertainty regarding the clinical effectiveness and long-term costs (71).

6.3. R&D costs

An ATMP administration may be very costly, for example Chondrocelect® requires 2 surgical operations which leads to high costs of clinical trials (62). Therefore, higher costs of development and manufacturing are associated with ATMPs than with chemical pharmaceuticals.

However, ATMPs are mainly developed in universities (or small start-up derivatives), tissue banks and small and medium enterprise (SME) (7). Those institutions operate with limited budgets and economic boundaries.

In addition, academic developers do not have sufficient knowledge on regulatory requirements for ATMPs and complex regulatory pathways that will lead to substantial pressure on small enterprises.

6.4. Market access challenges & MA withdrawal

6.4.1. Health Technology assessments of approved ATMPs

European regulators tend to speed market access of such therapies through accelerated pathways, but health technology assessment (HTA) bodies/payers are increasingly scrutinizing the incremental value of these products. ATMPs with high price tag are struggling to achieve reimbursement and enter the market. The main hurdles facing the ATMPs at the market access level are:

- Evidence may likely be short term and extrapolation of outcome will be needed,
- Immature data at time of approval,
- No long-term data,

- Heterogeneous outcomes,
- Heterogeneous population,
- Uncertainties,
- Patients enrolled in clinical trials may not be representative of patients in clinical practice.

To date, among 9 approved ATMPs in EU, 7 out of the 9 were assessed in at least one European country. Zalmoxis® and Spherox® newly approved are not yet assessed.

- Some approved ATMPs price tags(62):
  - Chondrocelect: 20,000€
  - Glybera: 1.1 million €
  - Provenge: 93,000$ (in US)
  - Imlygic: 65,000$ (in US)
  - Strimvelis: 594,000€ (Italy)

The Health Technology Assessments (HTA) of approved ATMPs in the 5 EU countries: France, UK, Germany, Italy and Spain will be presented when available.

6.4.1.1. Chondrocelect®

Chondrocelect® succeeded to obtain reimbursement in Belgium (2011) Netherlands (2012) and in Spain (2013) on the basis of a risk-sharing agreement (72-74).

- France: Chondrocelect® was not recommended by the French health ministry (Haute autorité de santé: HAS) in May 2013; HAS considered that it has insufficient actual benefit (AB) to justify its reimbursement by National Health Insurance in the indication of the MA, the efficacy/adverse effects ratio has not been clearly established (75).

- United Kingdom (UK): In August 2015, after the consultations and scoping workshop, NICE published the block scoping report for Chondrocelect® and MACI® with the following remit: ‘’*To appraise the clinical and cost-effectiveness of autologous chondrocyte implantation within the applicable licensed indications for repairing symptomatic articular cartilage defects of the knee*.” If ministers decide to refer these technologies, they are formally referred to NICE for appraisal along with the final remit (76).

- Germany: Chondrocelect® obtained in 2009 a New Diagnostic and Therapeutic Procedures agreement (Neue Untersuchungs- und Behandlungsmethoden or NUB) status 1 from the Institute for the Hospital Remuneration System (Institut für das Entgeltsystem Im Krankenhaus or IneK). Hospitals submit individually NUB applications for Chondrocelect® and negotiates budgets with the local sick funds (77).

6.4.1.2. Glybera®

Glybera® has been evaluated in France and Germany, but failed to achieve reimbursement in both countries.

- France: Glybera® was not recommended by HAS in November 2015. HAS considered that the actual benefit is insufficient, its benefit could not be established based on the clinical trials design (open label), small sample size and the absence of a sustained effect beyond 1 year (78).
- Germany: the German Health Technology Assessment process (AMNOG) and German Federal Joint Committee (G-BA) assessed Glybera® and granted it "unquantifiable additional benefit". Then, the positioning was changed to a hospital-only product, therefore direct price negotiations between hospitals and payers have place. So far, one single patient received Glybera® in Germany at Charité in Berlin in September 2015 (79).

6.4.1.3. MACI®

Germany: G-BA extended the suspension of the review and decisions on quality assurance of MACI® until December 31, 2019 waiting for additional data on long term safety (80).

6.4.1.4. Provenge®

- UK: in January 2015, NICE published the final appraisal for Provenge® stating: "*Sipuleucel-T is not recommended within its marketing authorization for treating adults who have asymptomatic or minimally symptomatic metastatic non-visceral hormone-relapsed prostate cancer for which chemotherapy is not yet clinically indicated."* NICE considered that Provenge® was not cost-effective, it did not meet the criteria for end-of-life consideration. The committee had uncertainties regarding the indirect comparison with arbiterone , in addition, NICE concluded

that the trials did not show that sipuleucel-T delayed disease progression compared with placebo (81) .

- Germany: G-BA concluded that the clinical added benefit of Provenge® is "non-quantifiable"(82).

6.4.1.5. Holoclar®

So far, Holoclar® is only reimbursed in France; in July 2016, HAS has given a positive recommendation for the reimbursement of Hololcar®. The reimbursement rate is 65% (83) .

The actual benefit was considered important in the treatment of moderate to severe limbal stem cell deficiencies fulfilling the following criteria:

- Superficial cornea neovascularization in at least 2 quadrants in one of the 2 eyes
- Central cornea problem
- Altered visual acuity

The actual benefit was considered insufficient for other conditions not fulfilling the criteria above.

- UK: In August 2017, NICE recommended Holoclar® for the treatment of moderate to severe limbal stem cell deficiency after eye burns; it should be used to treat 1 eye only after a conjunctival limbal autograft or in case of insufficient tissue for a conjunctival limbal autograft or it is contraindicated. A discount was agreed with the company.
  The treatment of both eyes is recommended for research only and when there is not enough tissue for a conjunctival limbal autograft.
  "Moderate to severe limbal stem cell deficiency is defined by the presence of superficial corneal neovascularisation in at least 2 corneal quadrants, with central corneal involvement, and severely impaired visual acuity" (84).

- Germany: Holoclar® has been assigned NUB status 4. NUB is an individualized hospital specific additional payment for innovative products. Status 4 means that there is a lack of lack of scientific evidence (85).

6.4.1.6. Imlygic®

So far, UK is the only European country that achieved Imlygic® assessment, it is ongoing in other countries.

- UK: NICE considered that Imlygic® was not cost-effective. However, after providing more evidence from the manufacturer and agreeing on a straight confidential discount , NICE approved the use of Imlygic® for patients for whom treatment with systemically administered immunotherapies is not suitable (86).
- Germany: the German health technology assessment body (IQWiG) concluded that the manufacturer dossier contained no data suitable for assessment. G-BA defined 3 comparators based on the treatment previously taken by the patients. These comparators were not used in the trials (87).

6.4.1.7. Strimvelis®

Strimvelis® has been evaluated in Italy and has yet to be evaluated in other European countries.

Italy: the Italian medicines agency (Agenzia Italiana del Farmaco or AIFA) approved the reimbursement of Strimvelis® at a price of €594,000 with risk-sharing scheme with payback in case of treatment failure (8).

6.5. MA withdrawal

After obtaining a marketing authorization, ATMPs MA holders are struggling to achieve reimbursement in Europe. Regulators are trying to accelerate the regulatory process, whereas payers are scrutinizing the value of the new innovative products, they tend to not recommend ATMPs for reimbursement mainly because of immature data or postpone their final decisions due to limited data.

Market access delays led to delay in return on investment of the ATMP manufacturers that started to face economic difficulties. Indeed, 3 out of the 9 MA granted for ATMPs in EU have been withdrawn so far (

Table **7**).

6.5.1. MACI®

Due to commercial reasons, MACI® marketing authorization holder closed the manufacturing site in Denmark on September 2014. Consequently, the manufacturing licence was withdrawn. CAT evaluated the case of MACI and issued a draft opinion that was adopted by CHMP and sent to the European Commission. The marketing authorization was suspended on 19 November 2014 until a new manufacturing site is registered in the EU (88).

6.5.2. Provenge®

The manufacturer of Provenge®, Dendreon, went bankrupt due to commercial reasons. Multiple factors contributed to the bankruptcy of Dendreon like the market access barriers and its high price (89). On 6 May 2015, the European Commission withdrew the marketing authorisation for Provenge® after the request of Dendreon (90).

6.5.3. Chondrocelect®

Chondrocelect®, approved in 2009, could not obtain reimbursement in the key EU countries. Therefore, the manufacturer, Tigenix, decided to withdraw the MA due to commercial reasons (91). Continuing to invest in an approved ATMP and pay to provide additional data is associated with uncertainties whether payers will approve it for reimbursement after evidence generation. Tigenix decided to concentrate its resources and capabilities on its allogeneic stem cell platforms, its upcoming Cx601 Phase III US trial and its other clinical stage assets.

6.5.4. Glybera®

In April 2017, Glybera® MA holder – Uniqure - announced that Glybera® MA renewal will not be pursued. Therefore, the MA of this first gene therapy will expire in October 2017. This withdrawal was due to the limited market access of Glybera® and not related to any risk-benefit concerns. Uniqure decided to focus their financial resources on the development of another therapy (92).

6.6. Case study: Provenge®

Provenge® was developed by Dendreon to treat patients with metastatic advanced prostate cancer. It was the first vaccine for cancer, first alternative to chemotherapy for patients with prostate cancer and the first personalized medicine for cancer.

In May 2007, the Food and Drug Administration (FDA) in the United States (US) rejected Dendreon application considering that Provenge® did not achieve the primary endpoints (progression free survival) in the 2 Phase III trials.

In 2010, Provenge® was approved by FDA for the treatment of asymptomatic or minimally symptomatic mCRPC based a new clinical trial that showed 4 months survival gain versus placebo (25.8 vs. 21.7 months) and no improvement in progression-free survival.

In September 2013, Provenge® was granted a MA in EU with a narrower indication: "patients with non-visceral metastases and who have not yet received chemotherapy". Provenge® was only launched in UK and Germany.

Provenge® was priced at $31,000 per infusion in the US at the time of launch; the entire cost of treatment is $93,000 for 3 doses. In March 2011, Centers for Medicare & Medicaid Services (CMS) approved reimbursement of Provenge® which simplified reimbursement in the whole labeled indication.

The main issue was the slow uptake of the drug; US oncologists and urologists said reimbursement issues have contributed to the slow uptake of the treatment-but the complexity of administering the drug is also a deterrent; in addition Provenge® was considered expensive. Furthermore, Provenge® sales declined in the quarter immediately following Zytiga®'s approval in the pre-chemotherapy setting.

Dendron's predictions from the sales of Provenge® were 4 billion dollars per year. It achieved net revenue of $300 million from the sale of Provenge® in 2014, compared to $283.7million in 2013 and $325.3million in 2012. The company had $2.3 billion in losses.

As a consequence, Dendreon withdrew Provenge® MA in EU and Dendreon was acquired by Valeant in March 2015 (89). Provenge® is still available in US.

In June 2017, Valeant completed the sale of Dendreon to Sanpower group for $819.9 million in cash, as part of realignment of its product portfolio strategy (93).

Table 7. Approved ATMPs and their current approval status

Brand name	Composition	Indication	Marketing authorization	Current approval

				status
Chondrocelect®	Autologous chondrocytes	Repair of single symptomatic cartilage defects of the femoral condyle of the knee	October 2009	Withdrawn in July 2016
Glybera®	Alipogene tiparvovec	Lipoprotein lipase deficiency	October 2012	Authorized (will be withdrawn in October 2017)
MACI®	Matrix-applied autologous chondrocytes	Repair of symptomatic, full-thickness cartilage defects of the knee	June 2013	Suspended in December 2014
Provenge®	Sipuleucel-T	Asymptomatic or minimally symptomatic metastatic castrate resistant prostate cancer adults in whom chemotherapy is not yet clinically indicated	September 2013	Withdrawn in May 2015
Holoclar®	Autologous human corneal epithelial cells	Moderate to severe limbal stem cell deficiency	February 2015	Authorized
Imlygic®	Talimogene laherparepvec	Regionally or distantly metastatic unresectable melanoma (Stage IIIB, IIIC and IVM1a)	December 2015	Authorized
Strimvelis®	Autologous CD34+ cells transduced to express ADA	Adenosine deaminase deficiency	May 2016	Authorized
Zalmoxis®	Allogeneic T cells genetically modified	Add-on treatment in adults who have received a haematopoietic stem cell transplant from a partially matched donor	August 2016	Authorized
Spherox®	Spheroids of human autologous matrix-associated chondrocytes	Repair the symptomatic articular cartilage defects of the femoral condyle and the patella of the knee (International Cartilage Repair Society [ICRS] grade III or IV) with defect sizes up to 10 cm2	July 2017	Authorized

Summary:

ATMP is a class of novel biopharmaceuticals that encompasses: TEP, sCTMP, GTMP and combined products. These therapies hold a promising therapeutic potential for many chronic and disabling diseases in areas with critical unmet needs. The European

Commission established a regulation to harmonize the evaluation of these therapies and ensure their efficacy and safety.

ATMPs are facing different challenges at the R&D level as well as commercialization and market access level. Payers are scrutinizing the incremental benefit of these drugs because of the high price claimed by their manufacturers. Indeed, those innovative promising therapies are very high-priced and may threaten the sustainability of healthcare system. So far, 9 ATMPs have been granted a MA in EU among which 4 MA were withdrawn, however this field is in continuous evolution. In the next chapter, the magnitude of the ATMP pipeline will be evaluated.

Chapter 2: The Magnitude of ATMPs Pipeline

1. Introduction

ATMPs constitute an innovative class of heterogeneous research driven biopharmaceuticals expected to bring important health benefits. These therapies aim to radically treat the causes of the diseases instead of only relieving the symptoms, they actually have a huge potential for dramatically controlling or curing many chronic disabling diseases and injuries.

Cell therapies have proven efficacy in treating myocardial infarction (94), Alzheimer's disease, Parkinson's disease (95), several cancers (96) and many other diseases. Gene therapies also may be effective on a wide range of previously untreated diseases such as haematological, ocular, neurodegenerative diseases and several cancers (97). For example, Adeno-associated AAV2 vectors carrying the therapeutic gene (RPE65) intra-retinal injection resulted in improved vision for people with Leber's Congenital Amaurosis (98, 99). Murine γ-retroviral vectors have also been employed in gene therapy trials of Adenosine deaminase deficiency (ADA-SCID), a fatal primary immunodeficiency with impaired T-, B-, and NK-cell development (100). Tissue engineered products are mainly used as regenerative therapy to enhancing wound repair and replacing damaged bone and cartilage (101). These products create therefore a high hope for reshaping the progression or the disability associated to multiple diseases including option for curing or reversing disease known as untreatable today or just subject to symptomatic treatments. Today, this is the ATMP promise.

Maciulaitis R. et al. (2012)(7) identified 318 clinical trials for ATMPs registered in the European Union Drug Regulating Authorities Clinical Trials (EudraCT) database between 2004 and 2010 . Beside Maciulaitis R. et al. (2012), Trounson A. et al. (2015)(102) showed the progress in developing stem cells therapies and the challenges facing them. Bisson I. et al. (2015) (103) identified 41 ongoing cell therapy clinical trials in April 2014 in United Kingdom (UK), the majority were in early phase and led by academics. Ginn SL et al, 2013 (104) showed that over 1800 gene therapy clinical trials were completed, ongoing or approved until 2012.

However, the development of ATMPs is a dynamic and fast-growing field; it has progressed greatly since the Maciulaitis R. et al, 2012, study identifying the ATMP studies in 2010. The 2010 cut-off date of Maciulaitis R. et al. is likely outdated, and a more up-to-date study evaluating the number of ATMPs in development would be valuable for the scientific society, policy decision makers and payers. This may help

payers to gain awareness to anticipate the hypothetical short and medium term budget impact of such products.

On the other hand, not all the products in development will successfully reach the market. Some clinical trials would be discontinued, terminated or withdrawn due to several reasons. Therefore, it would be of interest to estimate the rate of discontinuation of an ATMP clinical trial to evaluate the number that may reach the market. In addition, the development of these new therapies and high-quality randomized clinical trials is expensive and resource-demanding (105). The discontinuation of randomized clinical trials (RCT) wastes scarce resources. Therefore, it is critical on one hand to minimize the risk of trials discontinuation and on the other hand to estimate the risk of trials discontinuation to integrate this information in Go/No-Go decision. The rate of discontinuation is one of the components of the risk of failure rate. This risk is an important driver of the expected net present value that informs manufacturer prioritization to invest in a portfolio of products (106). A study of Kasenda B et al, 2014, (107) showed that the rate of discontinuation of Randomized Clinical Trials is 25%. No or very few ATMPs were included because the concept of ATMPs is recent and the trials included in this study were registered between 2000 and 2003; moreover potential ATMPs were not reviewed separately. To our knowledge, there are no data on the rate of discontinuation of ATMPs clinical trials.

The aims of the study described in this chapter were to evaluate the magnitude of ATMPs pipeline and to estimate the number and characteristics of discontinued ATMPs clinical trials in order to evaluate the discontinuation rate.

2. Materials and Methods

The work was divided in 3 parts:

- The first part mapping the number of ATMP clinical trials worldwide,
- The second part was mapping the number of gene therapies clinical trials worldwide to complete the first part of the study,
- The third part was identifying the probability of discontinuation of ATMPs clinical trials.

2.1. Materials and methods: ATMPs clinical trials mapping

2.1.1. Data collection

Two independent researchers retrieved all clinical trials of ATMPs conducted during the time period from 1999 to June 2015 using three clinical trials databases:

- Clinicaltrials.gov,
- International Clinical Trials Registry Platform (ICTRP) of the World Health Organisation (WHO),
- European Union Drug Regulating Authorities Clinical Trials (EudraCT).

The same combinations of keywords were used for the three databases searches:

- For cell therapies and tissue: “cell therapy”; “stem cell”; “cord blood”; “umbilical cord”; “bone marrow”; “cancer vaccine”; “Tissue engineering”; “engineered cell”; “tissue engineered”; “mesenchymal cell”; “somatic cell”; “allogeneic cell”; “viable cell”.

- For gene therapies: “gene therapy”; “recombinant nucleic acid”; “DNA therapy”; “cDNA”; “recombinant DNA”; “nucleic acid therapy”; “gene transfer”; “virus delivery”; “cancer immunotherapy”; “RNA therapy”; “tumor vaccine”; "genetic therapy”; “plasmid DNA”; “oligonucleotides”; “genetically modified microorganisms”; “genetically modified organisms”; “genetically modified cells”.

2.1.2. Data extraction and selection

Specific data extraction forms were designed using Microsoft Excel 2010 to extract the following clinical trials data:

- Registration number,
- Date of registration,
- Title,
- Status,
- Phase,
- Study design,
- Target enrolment number,
- Sponsor,

- Disease,
- Last update date.

Duplicate studies with the same registration number were removed as well as all pre-clinical studies, phase 0 (exploratory) studies, pilot studies and observational studies.

We excluded trials that were not for ATMPs and we classified the remaining trials by ATMP class, based on the definition of ATMP provided by the European regulation EC N° 1394/2007(24) , i.e:

Gene therapy medicinal products should fulfil the three following criteria:

- biological origin,
- contains recombinant nucleic acid(s)
- the therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains or to the product of genetic expression of this sequence.

sCTMPs and TEP both contain or consist of engineered cells or tissues. To be considered engineered, cells or tissues should fulfil at least one of the following criteria:

- Substantial manipulation: biological characteristics, physiological functions or structural properties relevant for the intended regeneration, repair or replacement are achieved during their manipulation.
- Non-homologous use: the cells and tissues are not intended to be used for the same essential function (s) in the recipient and the donor.

sCTMPs are presented as having properties for, or used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues. TEPs are presented as having properties for, or are used in or administered to human beings with a view to regenerating, repairing or replacing a human tissue (108, 109) .

The classification was performed by two reviewers and discrepancies re-analysed. In case of persistent discrepancy, it was resolved by consensus and in case of failure by arbitration with the support of a senior researcher skilled in pharmaceutical sciences and biologics.

2.1.3. Data analysis

The data were sorted out by:

1) Sponsor status:

- Commercial,
- Non-commercial : 5 settings:
  - Hospital,
  - University,
  - Institute,
  - Medical centre,
  - Government.

2) Development phase

3) Pathology:

- Cancer,
- Cardiovascular
- Haematology,
- Musculoskeletal ,
- Immune system/inflammation,
- Neurology,
- GI/diabetes/metabolism,
- ophthalmology,
- pulmonology,
- Dermatology: wounds, ulcers,
- Others.

4) Date range: the following date range was considered to assess the evolution overtime of the number of clinical trials with ATMPs: 1999-2003; 2004-2010; 2011-2015

5) Last update date was recorded for each trial

6) Target enrolment number was classified according to the following range <25, 25-50, 51-100, >100.

2.1.4. Mapping of gene therapies trials: Materials and Methods

In this study, an additional clinical trials database especially for gene therapies was used. Gene therapy clinical trials data were extracted from an interactive publicly available database: "Gene Therapy Clinical trials worldwide" provided by the journal of Gene Medicine.

The sources of the data in this database were official agency sources:

- Research Administration and Compliance (RAC),
- Gene Therapy Advisory Committee (GTAC),
- The published literature and presentations at conferences and from information provided by investigators or trial sponsors.
- Information on the trials performed in the US was derived directly from the Office of Biotechnology Activities (OBA) /RAC website.

At time of manuscript writing, data were last updated in February 2016. The database presented information on individual gene therapy trials performed worldwide including:

- Trial country,
- Principal investigator,
- Disease category,
- Indication,
- Vector used,
- Gene transferred,
- Gene type,
- Clinical phase,
- Trial status,
- The year trial approved/initiated.

We extracted data from clinical trials that started between 1989 - 2015 including:

1) Number of trials per year between 1989 and 2015;
2) Countries where the trials were conducted:
    - Multi-country,
    - United states,
    - United kingdom (UK),
    - Germany,

- China,
- France ,
- Switzerland,
- Japan,
- The Netherlands,
- Australia,
- Canada,
- Others.

3) Diseases targeted by gene therapies:

- Cancer diseases,
- Cardiovascular diseases,
- Infectious diseases,
- Inflammatory diseases,
- Monogenic diseases: cystic fibrosis, Huntington's disease, Fanconi anaemia, Gaucher disease , severe combined immunodeficiency (scid), haemophilia A and B, hurler syndrome, hunter syndrome and others,
- Neurological diseases,
- Ocular diseases,
- Others;

4) Vectors used for gene delivery:

- Adeno-associated virus,
- Adenovirus,
- Retrovirus,
- Vaccinia virus,
- Lentivirus,
- Herpes simplex virus,
- Lipofection,
- Naked/plasmid DNA,
- Poxvirus,
- RNA transfer.

5) Trials status: closed, withdrawn, on clinical hold, conditional approval, cancelled, under review, submission not completed
6) Phases of development: I, I/II, II, II/III, III, IV, or single subject.

2.2. Materials and methods: Rate of discontinuation

In this study, the data extracted in the first study was used. The data was extracted from 3 different clinical trials databases: Clinicaltrials.gov, ICTRP of the World Health Organisation (WHO), and EudraCT. The same combinations of keywords were used for the three databases searches. (For more details on materials and methods, see 2.1)

We searched for:

- Withdrawn, terminated or prematurely ended ATMPs clinical trials that will be referred to as "discontinued trials" in this study conducted during the time period from 1999 to June 2015.
    - Withdrawn trials: The clinical study was stopped before enrolling the first participant (110),
    - Terminated trials: The clinical study has stopped recruiting or enrolling participants early and will not start again. Participants were no longer examined or treated (110),
    - Prematurely ended: the clinical study was ended before the administration of the last treatment dose to the last patient according to the last version of the protocol.
- Ongoing and completed trials conducted from 1999 to June 2013 with a recent last update date (last update date > May 2014).

Data extraction forms were designed using Microsoft Excel 2010 to extract: registration number, date of registration, title, status, phase, study design, target enrolment number, sponsor, disease, and last update date.

Duplications were removed as well as the therapies that were not classified as ATMPs. We classified the remaining trials by ATMPs type, based on the definition of ATMP provided by the European regulation EC N° 1394/2007(24).

The data were sorted out by:

- Type of ATMPs: sCTMPs, GTMPs or ,TEPs , and combined ATMPs
- Sponsor status : commercial, non-commercial. For non-commercial sponsors, the corresponding clinical trials were classified into 5 settings: hospital, university, institute, medical centre, government
- Development phase: phase 1, 1/2, 2, 2/3, 3

- Pathology: Cancer, Cardiovascular, Musculoskeletal, Immune system/inflammation, Neurology, Gastro-intestinal/ diabetes/ metabolism, Ophthalmology, pulmonology, Dermatology: (wounds, ulcers), others.

We calculated the rate of discontinuation of ATMPs clinical trials using:

Probability of discontinuation of ATMP trial

$$= \frac{\text{Number of discontinued trials}}{(\text{Number of discontinued trials} + \text{Number of ongoing and completed trials})}$$

We calculated the rate of discontinuation of trials for every category of ATMPs, in every phase and by sponsor status.

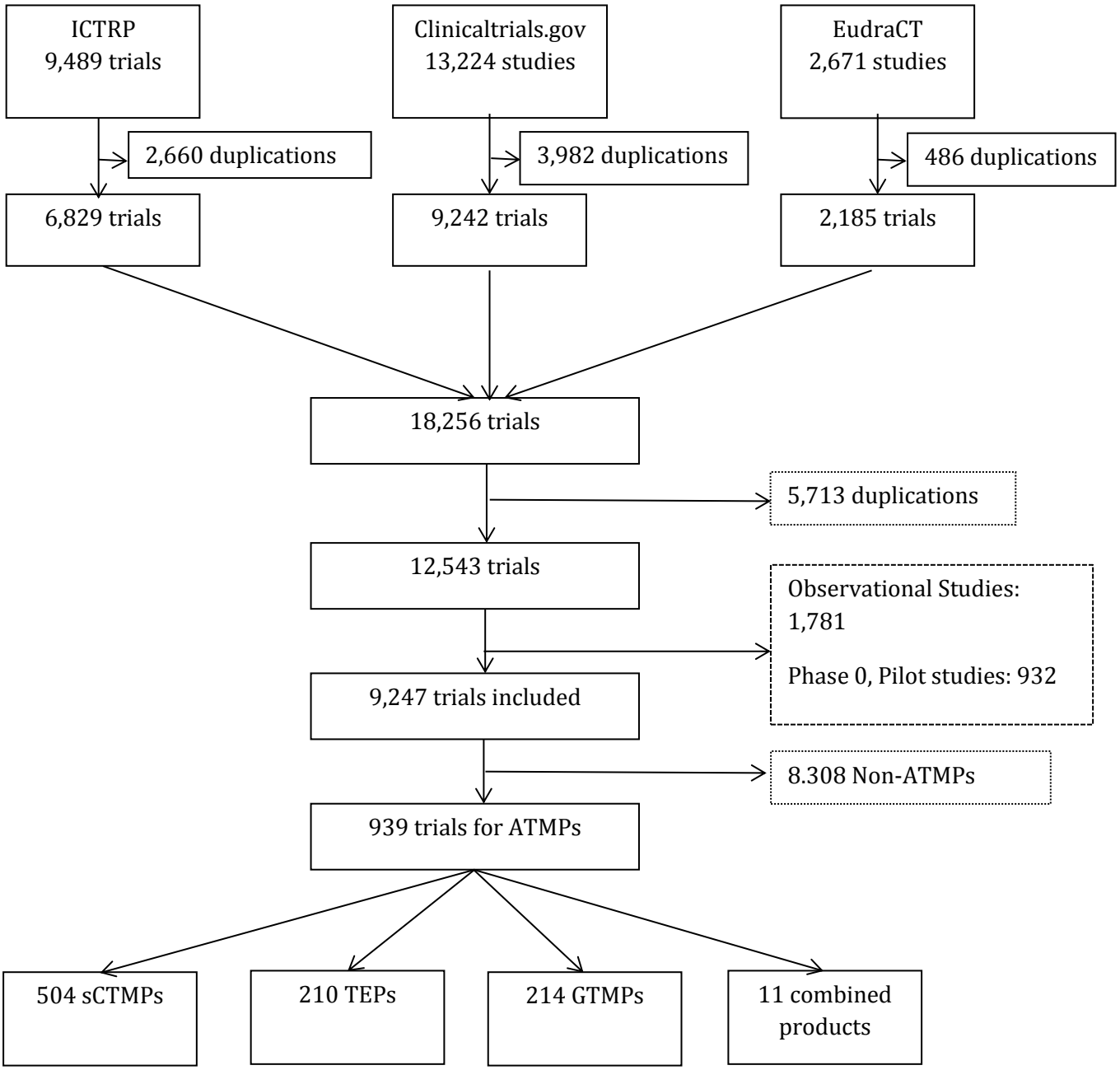
3. Results

3.1. Results of ATMP Mapping

3.1.1. Search results

The search strategy resulted in a total of 25,384 trials extracted from 3 different trials databases: clinicaltrials.gov, EudraCT and ICTRP. After removing duplicates (12,841 trials), observational studies (1,781 trials), phase 0 studies, pilot studies as well as terminated or withdrawn studies (932 trials), 9,247 trials were considered for screening. As a result, based on the ATMP definition in the Regulation (EC) No 1394/2007, we identified 939 clinical trials investigating ATMPs.

Figure 13. Flow chart of clinical trials identification and inclusion

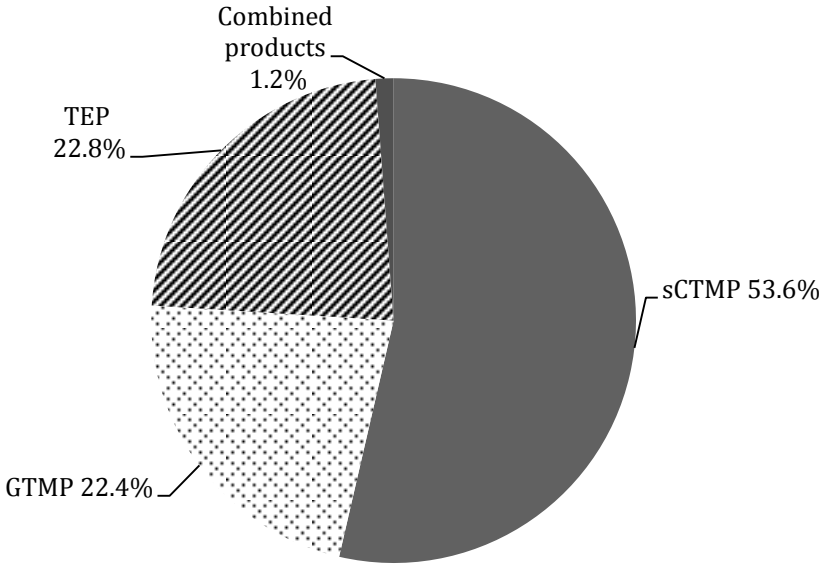


ATMPs: Advanced Therapy Medicinal Products, sCTMPs: Somatic Cell Therapy Products, TEPs: Tissue Engineered Products, GTMPs: Gene Therapy Medicinal Products, ICTRP: International Clinical Trials Registry Platform

3.1.2. ATMP class

Almost half of the medicinal products clinical trials identified in this study were trials for evaluating somatic cell therapies (53.6%), the remainder were either for tissue engineered products (22.8%), or gene therapies (22.4%). The combined products represented only 1.2% of the products (Figure 14).

Figure 14. ATMP in development classification

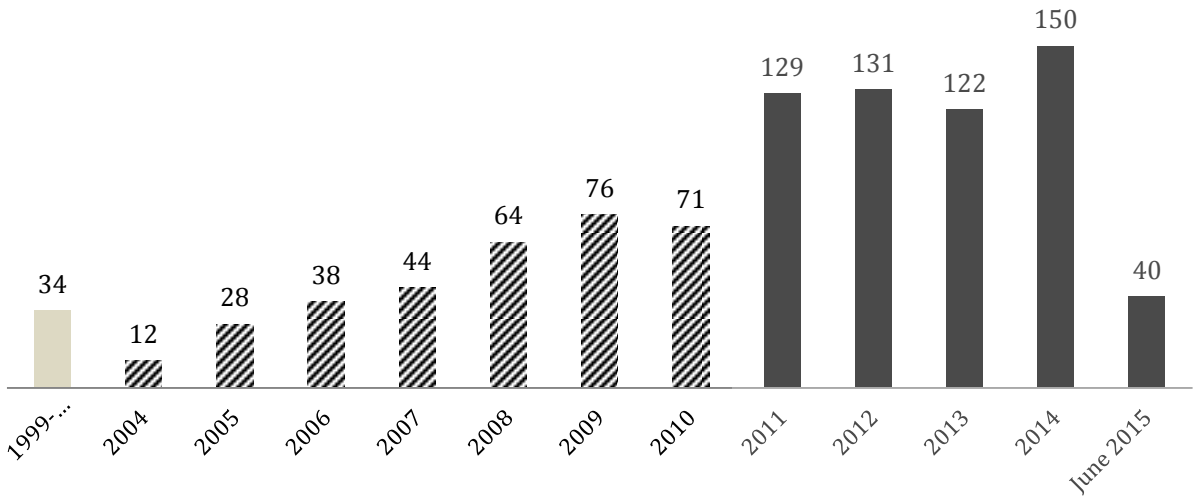


Percentages of gene therapy medicinal products (GTMPs), somatic cell therapy medicinal products (sCTMPs), tissue-engineered products (TEPs), and combined products.

3.1.3. Registration date and status

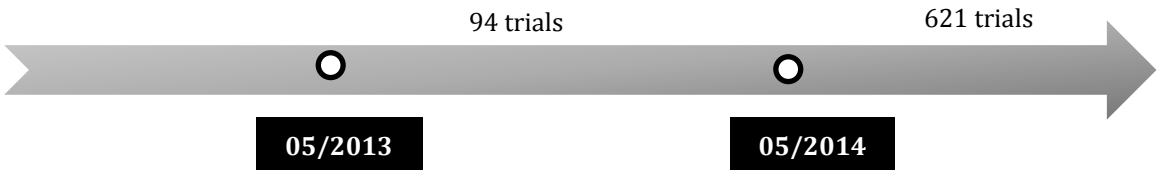
Overall, the results showed that the number of ATMPs clinical trials has been consistently growing over the past 15 years. Between 1999 and 2003, 34 trials were registered in the databases, compared to 333 in 2004-2010 and 572 trials in 2011-2015. Twelve trials were registered in 2004, this number has steadily increased over one decade to reach the highest peak in 2014 with 150 ATMP trials.

Figure 15. Number of ATMP trials from 1999-2015



Majority of the trials were still ongoing, 85% of the trials were ongoing and 15% were completed. Two-thirds of the ATMPs trials (621 trials) included had a recent last update date, suggesting that they are still active and 126 (13.4%) had an update date of two years or more (Figure 16).

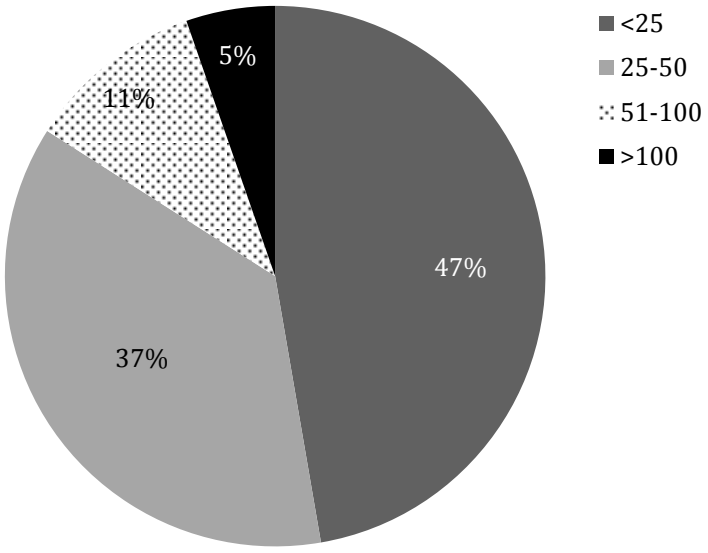
Figure 16. Last Update date of ATMPs trials



Note: The update date was not reported in 98 trials (10.5%) mostly because recently initiated studies.

Almost half of the trials extracted had a small sample size. Four-hundred-forty-four trials (47.2%) enrolled less than 25 patients (Figure 17).

Figure 17. Number of patients enrolled



3.1.4. Targeted disease

While these therapies are being developed to target several different diseases, oncology remained the dominant therapeutic area, accounting for 24.8% of the trials identified: Leukaemia/Lymphoma/myeloma (30.9%), skin cancer (10.3%), prostate cancer (9.9%), brain cancer (8.2%), cancer of the gastro-intestinal (GI) system (7.7%), bladder and renal cancer (6.8%), nasopharyngeal and lung cancer (4.7%), breast cancer (3.9%) , others (6.0%) and the type of cancer was not specified in 11.6% of the oncology trials.

Cardiovascular diseases represented the second biggest therapeutic area, representing 19.38% of the trials: Heart failure: ischemic and non-ischemic/ cardiomyopathy (31.3%), limb ischemia and peripheral arterial disease (24.2%), Myocardial infarction/Coronary Artery Diseases (23.6%), stroke (11.5%), and others (9.3%).

Many other disease areas were identified: inflammation (11.5%), musculoskeletal system diseases (10.5%), neurology (9.1%), gastro-intestinal disease, diabetes (5.2% all together), ophthalmology (4.7%), pulmonology (3.4%), dermatology (3.1%), haematology (2.1%) and other therapeutic areas (6.2%) (Table 8 and Table 9).

Others include X chromosome -linked inherited disease (58.6%), enzymes deficiency/lysosome (34.6%), infertility (1.7%), vocal cord (1.7%), ear membrane (3.4%).

Table 8. Diseases included in every disease area

Disease Area	Diseases	Number of trials
Cancer	Leukaemia/Lymphoma/myeloma	72 (30.9%)
	Skin cancer	24 (10.3%)
	Prostate cancer	23 (9.9%)
	Brain cancer	19 (8.2%)
	Gastro-intestinal system cancer	18 (7.7%)
	Bladder or renal cancer	16 (6.8%)
	Respiratory system (nasopharyngeal, lung) cancer	11 (4.7%)
	Breast cancer	9 (3.9%)
	Others	14 (6.0%)
	Blanks (type of cancer not specified)	27 (11.6%)
Total		**233**
Cardiovascular and blood diseases	Heart failure: ischemic and non-ischemic/ cardiomyopathy	57 (28.2%)
	Limb ischemia and peripheral arterial disease	44 (21.8%)
	Myocardial infarction/Coronary Artery Diseases	43 (21.3%)
	Stroke	21 (10.4%)

	Anaemia/ sickle cell thalassemia	15 (7.4%)
	Haemophilia	5 (2.5%)
	Others	17 (8.4%)
Total		**202**
Musculoskeletal diseases	Bone defects	46 (46.5%)
	Muscular dystrophy	28 (28.3%)
	Cartilage defects	22 (22.2%)
	Tendinopathy/ ligament defects	3 (3.0%)
Total		**99**
Inflammation/Immune system	Diverse inflammations	39 (36.1%)
	Arthritis / spondylitis	29 (26.8%)
	Crohn disease	23 (21.4%)
	Lupus	4 (3.7%)
	Others	13 (12.0%)
Total		**108**
Others	X chromosome -linked Inherited disease*	34 (58.6%)
	Enzymes deficiency/lysosome	20 (34.6%)
	Infertility	1 (1.7%)
	Vocal cord	1 (1.7%)
	Ear membrane	2 (3.4%)
Total		**58**

* X-linked chronic granulomatous disease XCGD, Wiskott-Aldrich syndrome WAS

The majority of identified ATMP trials were in early stages of development, as shown in Table 9, with 64.3% of the trials in phase I, I/II, 27.9% in phase II, II/III and 65 trials (6.9%) were in phase III.

The quarter of phase I and I/II trials are targeting cancer, 17.2% for cardiovascular diseases and around 10% for immunology and inflammation, musculoskeletal diseases and neurology.

Similarly, cancer and cardiovascular diseases are targeted by around 25% of phase II and II/III trials each. 27.8% of phase III trials are ATMPs targeting cancers and 16.7% cardiovascular diseases. (Table 9)

Table 9. Classification of ATMPs trials by disease area and phase of development

	Phase I and I/II	Phase II and II/III	Phase III	NA	Total
Cancer	146 (62.7%)	69 (29.6%)	18 (7.7%)		**233 (24.8%)**
Cardiovascular & blood diseases	120 (59.4%)	71 (35.2%)	11 (5.4%)		**202 (21.5%)**
Immune system/ inflammation	68 (62.9%)	29 (26.9%)	9 (8.4%)	2 (1.8%)	**108 (11.5%)**
Musculoskeletal system	59 (59.6%)	25 (25.3%)	9 (9.1%)	6 (6.0%)	**99 (10.5%)**

Neurology	61 (71.8%)	23 (27.06%)	1 (1.2%)		**85(9.1%)**
GI diseases & diabetes	25 (51.0%)	15 (30.6%)	8 (16.3%)	1 (2.1%)	**49(5.2%)**
Ophthalmology	34(77.3%)	7 (15.9%)	3 (6.8%)		**44 (4.7%)**
Pulmonology	25 (78.1%)	6 (18.7%)	1 (3.2%)		**32 (3.4%)**
Dermatology	19(65.5%)	7(24.1%)	3(10.4%)		**29 (3.1%)**
Others	47 (81.0%)	9(15.5%)	2(3.5%)		**58 (6.2%)**
Total	**604 (64.3%)**	**261 (27.9%)**	**65 (6.9%)**	**9 (0.9%)**	**939 (100%)**

GI: Gastro-intestinal, others include: X chromosome -linked Inherited disease, Enzymes deficiency/lysosome, Infertility, Vocal cord, Ear membrane

3.1.5. Sponsor status

Around third-quarter of the ATMP trials identified in this study were sponsored by non-commercial sponsors (74%). Non-commercial sponsors include mainly: universities (37%), hospitals (31%), and public or para-public research institutes (20%), and government and medical centres represented respectively 5% and 7% of non-commercial sponsors (Figure 18). The commercial sponsors, pharmaceutical companies, represented the quarter of the ATMP trials sponsors.

Interestingly, when comparing the sponsor status and the development phase, results showed that half of the trials sponsored by commercial sponsors were in early phases. This proportion rose to 70% for trials sponsored by non-commercial sponsors. Trials in phase III accounted for 4.4% and 14.1% of the trials sponsored by non-commercial and commercial sponsors, respectively (

Table **10**).

Figure 18. Sponsors of ATMPs clinical trials

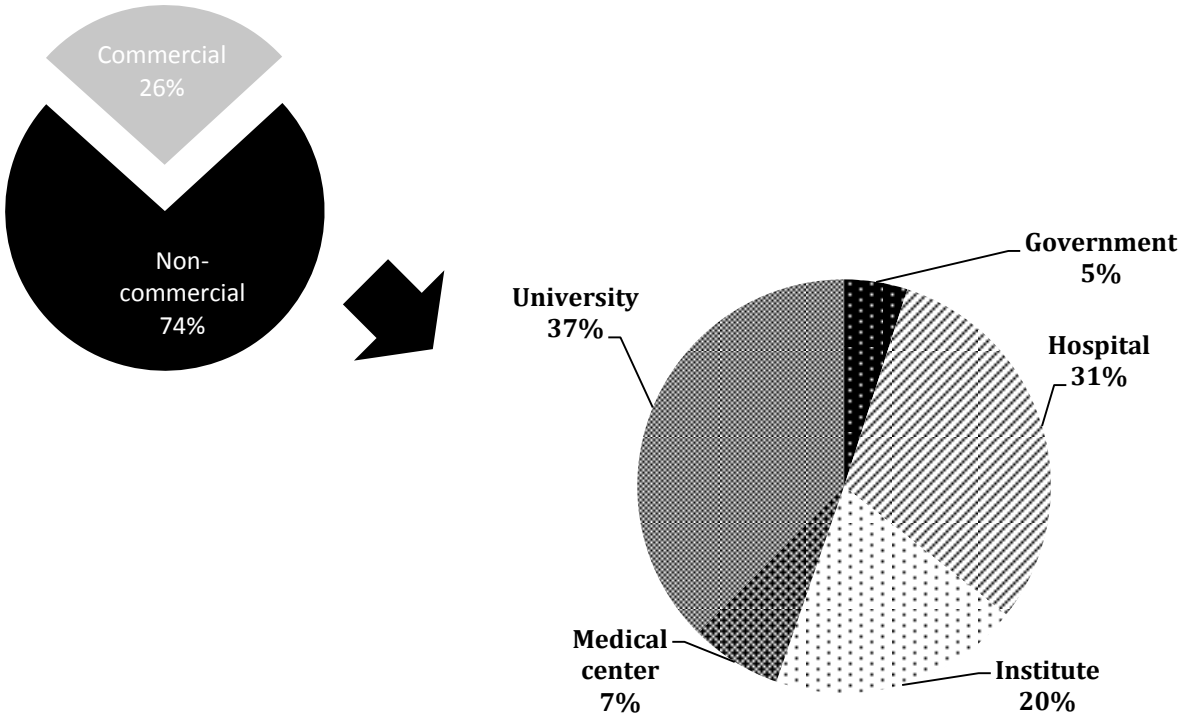


Table 10. Classification of the trials by sponsor status and phase of development

	Phase I and I/II	Phase II and II/III	Phase III	Phase not specified	Total
Commercial	124 (50.0%)	85 (34.3%)	35 (14.1%)	4 (1.6%)	248 (26.4%)
Non-commercial	480 (69.9%)	174 (25.3%)	30 (4.4%)	3 (0.4%)	687 (73.2%)
Sponsor not specified		2 (50.0%)		2 (50.0%)	4 (0.4%)
Total	604 (64.3%)	261 (27.9%)	65 (6.9%)	9 (0.9%)	939 (100%)

3.2. Focus on gene therapies: Results

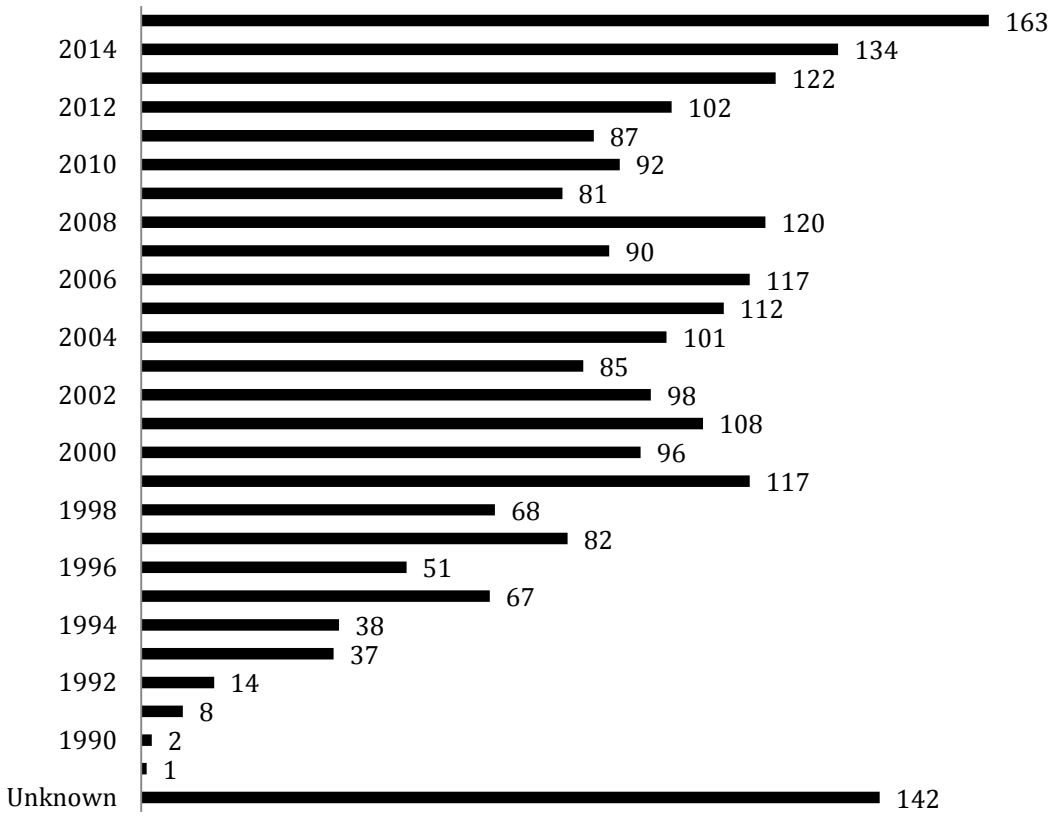
3.2.1. Number of gene therapy trials

Between 1989 and 2015, 2335 clinical trials were extracted from the database. Those gene therapy trials have been completed, ongoing or approved (but not started) worldwide.

After the first gene therapy trial in 1989, the number of clinical trials increased over time (Figure 19). This number did not rise steadily; the number of trials has progressively grown between 1989 and 1999 and it reached the first peak after one decade in 1999 with 117 gene therapy trials and the second peak after almost a second decade in 2008 with 120 trials, then the number of gene therapy trials dropped between 2009 and 2012.

Since 2012, the number of clinical trials has considerably increased, from 87 trials in 2011 to 102 trials in 2012 and continued to increase to reach its highest peak in 2015 (163 trials). The date was not specified for 142 trials

Figure 19. Number of gene therapy trials per year

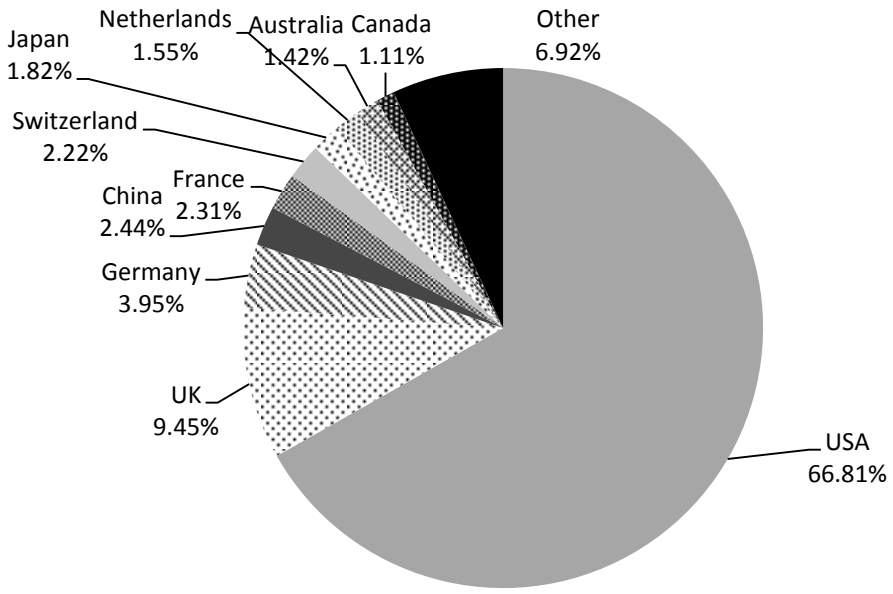


3.2.2. Countries undertaking the gene therapy trials

US undertook 66.81% of gene therapy clinical trials; all other countries participated in a small percentage of the trials: 9.45% in the UK, 3.95% in Germany and around 2% in each of these countries: Switzerland (2.22%), France (2.31%), Netherlands (1.55%), China (2.44%) and Japan (1.82%). Australia and Canada had the lowest proportion of

trials with 1.42% and 1.11% of the trials respectively. Other countries together constitute 6.92% of the gene therapy trials identified (Figure 20).

Figure 20. Distribution of gene therapy clinical trials by country

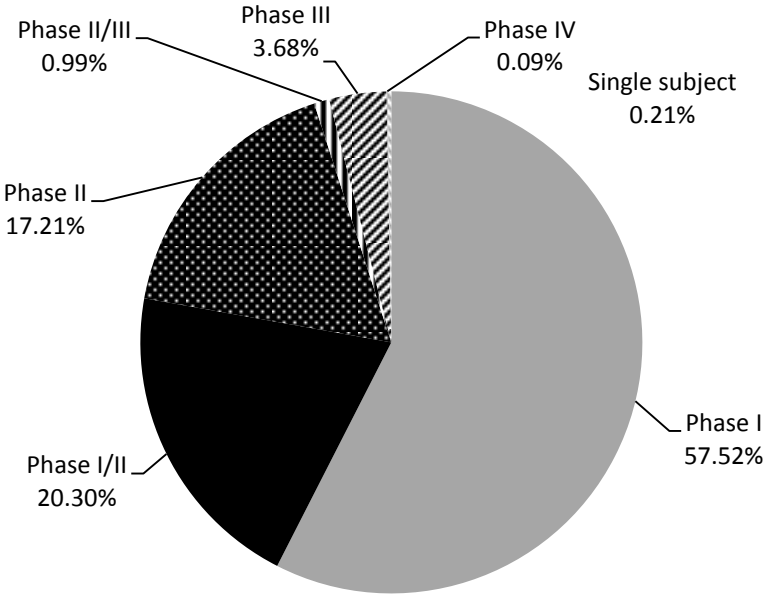


UK: United Kingdom, USA: United States of America

3.2.3. Phase of development

Almost 95% of the trials were in early phases of development; 57.52% of the trials were Phase I trials, 20.30% were Phase I/II, and 17.21% Phase II. Gene therapies in phase II/III, III, IV constituted only 5% of the trials (Figure 21) with respectively 0.99%, 3.68% and 0.09%. Single subject trials constituted 0.21% of the trials.

Figure 21. Phase of development of gene therapy clinical trials



3.2.4. Trials status

Seventy-two percent of the trials were ongoing, 24.83% were closed, and 1.20% of the trials were withdrawn. The 28 withdrawn trials (1.2%) were related to products in early phases of development, 42.86% in phase I.

Seventy-one phase III trials (82.5% of phase III trials) were ongoing, 11 trials were closed, 2 were cancelled, 1 was under review and 1 submission was not completed. The 2 Phase IV trials were ongoing (Table 11).

Table 11. Phase and status of gene therapy clinical trials

	Phase I	Phase I/II	Phase II	Phase II/III	Phase III	Phase IV	Single subject	Total
Open	970 (57.81%)	327 (19.49%)	288 (17.16%)	15 (0.89%)	71 (4.23%)	2 (0.12%)	5 (0.30%)	1678 (71.86%)
Closed	337 (58.10%)	129 (22.24%)	96 (16.55%)	7 (1.21%)	11 (1.90%)	-	-	580 (24.83%)
Withdrawn	12 (42.86%)	8 (28.57%)	8 (28.57%)	-	-	-	-	28 (1.20%)
On clinical hold	3 (42.86%)	3 (42.86%)	1 (14.28%)	-	-	-	-	7 (0.30%)
Conditional approval	9 (60.00%)	1 (6.67%)	5 (33.33%)	-	-	-	-	15 (0.64%)
Canceled	-	2 (33.33%)	1 (16.67%)	1 (16.67%)	2 (33.33%)	-	-	6 (0.26%)
Under review	10 (66.67%)	3 (20.00%)	1 (6.67%)	-	1 (6.67%)	-	-	15 (0.64%)
Submission not completed	2 (33.33%)	1 (16.67%)	2 (33.33%)	-	1 (16.67%)	-	-	6 (0.26%)

Total	1343 (57.52%)	474 (20.30%)	402 (17.21%)	23 (0.99%)	86 (3.68%)	2 (0.09%)	5 (0.21%)	2335 (100.00%)

3.2.5. Diseases targeted by gene therapy trials

The majority of gene therapy clinical trials targeted cancer diseases (64.41%). 52% of phase II/III trials, 66% of the phase III trials and all the Phase IV trials were for gene therapies targeting cancers (Table 12).

Monogenic diseases constituted the indication of 9.90% of the trials encompassing cystic fibrosis, Huntington's disease, Fanconi anaemia, Gaucher disease. Almost 8% of the trials targeted each of cardiovascular and infectious diseases.

Table 12. Number of gene therapy clinical trials by phase and indication

	Cancer diseases	Cardiovascular diseases	Gene marking	Healthy volunteers	Infectious diseases	Inflammatory diseases	Monogenic diseases	Neurological diseases	Ocular diseases	Others	Total
Phase I	886 (65.97%)	76 (5.65%)	42 (3.12%)	41 (3.05%)	106 (7.89%)	9 (0.68%)	128 (9.54%)	16 (1.19%)	14 (1.04%)	25 (1.86%)	1343 (57.51%)
Phase I/II	273 (57.59%)	34 (7.17%)	5 (1.06%)	2 (0.43%)	44 (9.28%)	-	78 (16.45%)	15 (3.16%)	10 (2.11%)	13 (2.74%)	474 (20.29%)
Phase II	271 (67.41%)	50 (12.44%)	3 (0.75%)	8 (1.99%)	22 (5.47%)	5 (1.24%)	13 (3.23%)	12 (2.98%)	8 (1.99%)	10 (2.49%)	402 (17.22%)
Phase II/III	12 (52.17%)	7 (30.43%)	-	-	-	-	4 (17.40%)	-	-	-	23 (0.98%)
Phase III	57 (66.28%)	10 (11.63%)	-	2 (2.32%)	6 (6.98%)	-	6 (6.98%)	-	1 (1.16%)	4 (4.65%)	86 (3.68%)
Phase IV	2 (100%)	-	-	-	-	-	-	-	-	-	2 (0.08%)
Single subject	3 (60%)	-	-	-	-	-	2 (40.00%)	-	-	-	5 (0.21%)
Total	1504 (64.41%)	177 (7.58%)	50 (2.14%)	53 (2.27%)	178 (7.62%)	14 (0.60%)	231 (9.90%)	43 (1.84%)	33 (1.41%)	52 (2.22%)	2335 (100%)

3.2.6. Vectors used

Adenovirus, retrovirus, naked/plasmid DNA were the most used vectors in the gene therapy trials with respectively 22.14%,18.76%, 18.03% of the trials . Adeno-associated virus vectors were used in 6.6% of the trials and vaccinia virus, lentivirus, lipofection were used as vectors in around 5% of the trials (Table 13).

Table 13. Vectors used for gene delivery

Vectors	Number (%)
Adenovirus	517 (22.14%)
Retrovirus	438 (18.76%)
Naked/Plasmid DNA	421 (18.03%)

Adeno-associated virus	155 (6.63%)
Lentivirus	134 (5.73%)
Vaccinia virus	123 (5.23%)
Lipofection	115 (4.92%)
Poxvirus	103 (4.41%)
Herpes simplex virus	84 (3.59%)
RNA transfer	43 (1.84%)
Unknown	75 (3.21%)
Others	127(5.44%)

3.3. Rate of discontinuation of ATMP trials

3.3.1. Rate of discontinuation

143 withdrawn, terminated or prematurely ended ATMPs clinical trials were identified between 1999 and June 2015 in the 3 clinical trials databases used in this study. The number of ongoing and completed clinical trials registered between 1999 and June 2013 with a recent last update date (last update date > May 2014) is 474 trials: 391 ongoing and 83 completed. Therefore, the estimated rate of discontinuation of ATMPs trials is 23.18%, calculated using the formula above (2.2)

Seventy-one point three percent of the discontinued trials were sCTMPs, 17.48% were TEP, 9.79% were GTMPs and 1.4% combined products.

The rate of discontinuation of cell therapies trials was 27.35%, it was 16.28% for gene therapies, 16.34% for TEP and 40% for combined products (Table 14).

Table 14. Rate of discontinuation in every category of ATMPs

	Discontinued trials	Ongoing and completed trials	Total	Rate of discontinuation
Somatic cell therapies	102 (71.33%)	271 (57.17%)	373 (60.45%)	27.35%
Gene therapies	14 (9.79%)	72 (15.19%)	86 (13.94%)	16.28%
Tissue engineered products	25 (17.48%)	128 (27.00%)	153 (24.80%)	16.34%
Combined products	2 (1.4%)	3 (0.64%)	5 (0.81%)	40%
Total	143 (23.18%)	474 (76.82%)	617(100%)	23.18%

3.3.2. Status of the trials and targeted therapeutic areas

Majority of the discontinued trials were in early phases of development: phase 1 and 1/2 (63.63%); 30.06% were in phase 2 and 2/3 and 6.30% were in phase 3.

The rate of discontinuation is 23% for phase 1, 1/2 and phase 3, and 26.54% for phase 2 and 2/3 (Table 15).

Table 15. Phase of development and therapeutic areas targeted by the discontinued trials

Therapeutic area	Phase 1 and 1/2	Phase 2 and 2/3	Phase 3	Total	Discontinuation Rate per disease area
Cancer	56 (64.40%)	27 (31.00%)	4 (4.60%)	87 (60.84%)	43.06%
Cardiology	16 (55.17%)	11 (37.93%)	2 (6.90%)	29 (20.28%)	19.20%
Immunodeficiency and Inflammation	4(57.14%)	1(14.29%)	2 (28.57%)	7 (4.89%)	10.45%
Musculoskeletal diseases	2 (50.00%)	1 (25.00%)	1 (25.00%)	4 (2.80%)	6.78%
Neurology	4 (80.00%)	1 (20.00%)	0	5 (3.49%)	11.11%
Gastrointestinal diseases and diabetes	1 (33.33%)	2 (66.67%)	0	3 (2.10%)	8.82%
Ophthalmology	2 (100%)	0	0	2 (1.40%)	9.52%
Pulmonology	1(100%)	0	0	1 (0.70%)	12.5%
Dermatology	2 (100%)	0	0	2 (1.40%)	15.38%
Others (XCGD, enzyme deficiency)	3 (100%)	0	0	3 (2.09%)	17.64%
Total	91 (63.63%)	43 (30.06%)	9 (6.30%)	143 (100%)	-
Discontinuation rate per phase	23.04%	26.54%	23.68%	-	-

The discontinuation rate in oncology is the highest (43%); 87 discontinued trials (60.84%) are for ATMPs targeting several cancers: 64.40% of them in phase 1 and 1/2 , 31.00% in phase 2 and 2/3, and 4.60% in phase 3. The second highest discontinuation rate is for cardiology trials (19.2%), 29 discontinued cardiology trials were identified, 55.17% of them are phase 1, 1/2 37.93% phase 2, 2/3 and 6.90% phase 3. The rates of discontinuation were lower for the rest of the disease areas: dermatology (15.38%), pulmonology (12.50%), neurology (11.11%), immunology (10.45%), ophthalmology

(9.52%), GI diseases (8.82%), musculoskeletal disease (6.78%) and others (XCGD, enzyme deficiency) 17.64% (Table 15).

3.3.3. Sponsors

Around the quarter (26.57%) of the withdrawn, terminated or prematurely ended trials were sponsored by commercial companies and 73.43% sponsored by non-commercial sponsors: 45.71% of them are universities, 30.48% institutes, 10.48% hospitals, 10.48% medical centres and 2.86% government.

The probability of discontinuation is almost the same for commercial and non-commercial sponsors, 24.52% and 22.73% respectively (Table 16).

Table 16. Rate of discontinuation by sponsor status

	Discontinued trials	Ongoing and completed trials	Total	Rate of discontinuation
Commercial sponsors	**38 (26.57%)**	**117 (24.68%)**	**155 (25.12%)**	**24.52%**
Non-commercial sponsors	**105 (73.43%)**	**357 (75.32%)**	**462 (74.88%)**	**22.73%**
Universities	48 (45.71%)	136 (38.10%)	184 (39.83%)	26.09%
Hospitals	11 (10.48%)	114 (31.93%)	125 (27.06%)	8.80%
Institutes	32 (30.48%)	57(15.97%)	89 (19.26%)	35.95%
Medical centres	11 (10.48%)	32 (8.96%)	43 (9.31%)	25.58%
Government	3 (2.86%)	18 (5.04%)	21 (4.54%)	14.28%
Total	**143 (23.18%)**	**474 (76.82%)**	**617(100%)**	**23.18%**

4. Limitations

Those studies carried some limitations. In the first study, the trials initiated before the implementation of the regulation may not be registered in the databases. However very few products that would qualify as ATMPs were in development at that time and therefore this limits the potential for this limitation to alter the outcome of this research. Second, a selection bias is possible, actually in clinicaltrials.gov and ICTRP, as the investigational products were not classified, we did the classification in the 4 types of ATMPs. We did the classification based on the ATMP definition in the regulation and only the composition of the product was visible during classification, this should have prevented significant misclassification.

The third study had different limitations. First, the reason for discontinuation is not available in the searched databases therefore some discontinuations may not be related to scientific/technical considerations. Second, another way to do this analysis would have been to identify all studies registered at a given time interval and to follow them up to discontinuation or completion. However, this may have significantly reduced the number of trials eligible as we need to have a sufficiently long follow-up to reach either completion or discontinuation as too many trials are still ongoing. Actually, 85% of the trials identified until June 2015 were still ongoing and 15% were completed. Alternatively, we limited our study to all ongoing and completed trials registered up to June 2013 and at all discontinuation up to June 2015. This means that we gave for the most recently registered trials at least two years follow- up to identify a potential discontinuation. This allowed considering more trials. In addition, the probability of transitioning between phases was not identified; this will be the objective of our future work. Third, some trials may have been discontinued trials but not necessarily reported by the sponsor however this may not be frequent. Fourth, ATMPs trials started before the ATMPs regulation may not be easily identified; however the first study showed that the number of ATMPs trials grew exponentially suggesting older trials carry a low impact on the overall results. These limitations suggest our estimated discontinuation rate may be slightly underestimated. However it is unlikely to significantly impact the results.

5. Discussion

ATMP is a class of novel biopharmaceuticals. Almost ten years after the adoption of the regulation, only 8 products have obtained regulatory approval in the EU and achieved limited success in securing reimbursement; this suggests a low impact of ATMPs to date on health insurance budget but also on patient health.

To identify the number and characteristics of ATMPs in development, we searched three different clinical trials databases and extracted the trials using specific keywords. We believe we have likely captured most of the ATMPs in development. We used the intervals of time: 1999-2003 which is the period before the initiation of EudraCT, 2004-2010 which is the interval of time between the initiation of EudraCT and the end of the first term of the CAT that was considered a milestone and the start of the Work Programme 2010 – 2015 by the CAT. The comparison between 2004-2010 and 2011-2015 can help to reflect the impact of the regulation on the development of ATMPs.

In addition, a study using one additional database special for gene therapies to focus on gene therapies in development was conducted. This database allows extracting data since 1989.

5.1. Number of trials

Our results are consistent with the results of Maciulaitis et al, 2012 (7), who identified 318 clinical trials for ATMPs between 2004 and 2010, in this same date cut-off, we identified 333 clinical trials. These 5% increase may be based on the use of multiple databases, or just to differences in classification of ATMPs. Actually *Maciulaitis R. et al, 2012* study was based on EudraCT database only; therefore it reflects the situation only in Europe, whereas we used 2 international databases (ICTRP and clinicaltrials.gov) in addition to EudraCT.

Our study showed that the number of ATMPs in development is increasing considerably, from 12 trials in 2004 to 150 in 2014. The ATMPs number surged substantially after 2010, from 79 in 2010 to 121 in 2011. Actually in 2009, the first ATMP has been granted a marketing authorization (53) , which may have progressively encouraged manufacturers to invest in R&D in this field. In addition, 2011 was the end of the transitional period of gene therapies and 2012 was the end of the transitional period for TEP, therefore manufacturers of products already on the market may have started to conduct clinical trials for these products in order to apply for the centralized MA and comply with the regulation.

Regarding the gene therapies trials, after the first gene therapy clinical trial was performed by Rosenberg A et al (111) in 1989, since then, companies started to invest increasingly in the development of these therapies and the number of gene therapy trials started to rise. However, this number did not increase steadily, drop-offs periods were the consequences of the publication of some reports on gene therapies adverse events (112-116). However, between 2012 and 2015, we noticed a prominent increase in the number of trials. Indeed, in 2012, Glybera® (alipogene tiparvovec) was the first gene therapy approved in EU for the treatment of adult patients diagnosed with familial lipoprotein lipase deficiency (LPLD) confirmed by genetic testing (54, 117) and suffering from severe or multiple pancreatitis attacks despite dietary fat restrictions. This therapy was granted a European orphan drug designation in March 2004 and was approved in EU under exceptional circumstances. Exceptional circumstances procedure was granted

due to the rarity of the disease, it has not been possible to obtain complete information about the medicine; every year, EMA will review any new information that becomes available to reassess the risk-benefit balance (118). The green light given to this first gene therapy may have been a turning point that led to investors' enthusiasm for the development of gene therapies. This may had stimulated pharmaceutical companies to invest more in the development of gene therapies, as reflected in the increasing number of clinical trials between 2012 and 2015 (521 trials between 2012 and 2015).

Coherently, a fourfold increase in the number of gene therapies since 2012 has been shown in a survey conducted in November 2015; the gene therapy products in development from preclinical phase to phase III and beyond worldwide identified were 418 products (119).

5.2. Trials phase, status and sponsors

In study 1 and study 2, the results were coherent; majority of the trials in both studies are ongoing (85%) and in early stages of development (92.2%: phase I, combined I/II, II, combined II/III). Two-thirds of the trials had recent update date suggesting that they are still active. It is not surprising that ATMPs trials are mainly in early stages of development; ATMPs are facing many challenges, their development needs important resources and huge workload, making their proceed to the final stages of development more difficult (120). Indeed, as we have shown, 75% of the sponsors are non-commercial sponsors like academics, hospitals and government. In addition, we showed that 53.8% of phase III trials are sponsored by commercial sponsors while they represent only 20% of phase I, I/II sponsors. In fact, non-commercial sponsors may have limited budget and limited experience to achieve the development of their products. Products initially developed by non-commercial sponsors may either be moved to spin-off organization or be licensed to a pharmaceutical industry to achieve their development in later phases and obtain marketing authorization. This could explain the gap in development status between commercial and non-commercial organizations. This assumption was not tested.

5.3. Countries undertaking clinical trials

Countries conducting the ATMPs clinical trials could not be identified in the first study. However, countries undertaking gene therapy clinical trials were extracted from the database "Gene Therapy Clinical trials worldwide" in the second study.

Gene therapy clinical trials were performed in 36 countries from the 5 continents. Four percent of these trials were performed in more than one country at the same time. The geographical distribution of trials had slightly changed from 2012 to 2015; America part had slightly increased to 68% (65.1% in 2012), whereas Europe part had slightly decreased to reach 24% instead of 28.3% in 2012. As in 2012, US undertook the majority of the trials (66.81%), and the UK was leading almost half of European gene therapy trials. A slow growth was observed in Asia, China reached 2.44% of the trials (1.4% in 2012) and Japan 1.82% (1.1% in 2012).

These data confirm the leading role of US in pharmaceutical innovation (121) . Actually it was widely agreed that the US dominated the pharmaceutical innovation since decades. This is driven by friendly environment to raise capital (122) (through angled business investors up to large investment organisation), the high funding level for health science research with organisations like U.S. National Institutes of Health (NIH) (123) and private foundations and organisations (124) , the broad experience in university/private research contracting as well as easiness of academic spin off (125) , and finally, a favourable tax scheme for research investment (126). After US, UK offers the similar friendly environment for entrepreneurs by offering research and development tax relief (127). It is much less the case for France and Germany, while research performance may not be inferior in those countries but less oriented toward research private valorisation and value development.

5.4. Gene types and vectors used for gene therapy

Different vector systems are used nowadays for gene delivery; there are 2 major categories: viral and non-viral vectors. Amongst the successful viral vectors, adenovirus and retrovirus are the most commonly used vectors (128) . This is coherent with our results as we had shown that adenovirus and retrovirus were used as vector in 22% and 18.7% of the trials respectively. Herpes simplex virus and lentivirus were recent candidates in gene delivery used in 3.6% and 5.7% of the trials respectively.

Non-viral vectors are chemical and physical systems including: cationic liposomes and polymers, particle bombardment, electroporation, ultrasound utilization. Non-viral vectors are less efficient than viral vectors but their availability and cost-effectiveness are more important than the viral vectors (129). Naked/ plasmid DNA is used in 18% of the trials as a vector.

Delivering therapeutic genes into patients' cells using efficient and safe vectors is considered as a challenge that gene therapies are facing. Viral vectors may cause undesirable effects by stimulating the host's immune system (130) and other problems such as: dose-related toxicity, pre-existing neutralizing antibodies, short-lived or insufficient transgene expression. Nonetheless, innovation is playing an important role to address this challenge. Reengineered adeno-associated virus (AAV) constitute the next generation of AAV. For example, AAV2.5 has an antigenically distinct profile and can evade neutralizing antibodies against both AAV1 and AAV2 capsids (131).

5.5. Disease areas

Our results showed that 939 ATMPs clinical trials are conducted in different disease areas. Cancer was the first indication targeted by ATMPs, almost the quarter of the trials are for ATMPs developed to treat cancers and 19.38% of the trials are for cardiovascular diseases. Similarly, cancer, cardiovascular diseases and monogenic diseases were the diseases targeted by the majority of gene therapies in development.

Cancer was the most common indication including different types of cancer: gynaecological, nervous system, gastrointestinal, genitourinary, skin, head and neck, lung, mesothelioma, haematological, sarcoma. Due to the widespread incidence of cancer that is increasing steadily, and the important medical needs in this field, manufacturers are incentivised to invest in the field of oncology; majority of the clinical trials in advanced phase of development are for gene therapies aiming to treat several cancers. Oncology represents a very attractive field for pharmaceutical companies as payers have shown a very high willingness to pay including for minor improvement, allowing a fast return on investment. Therefore, oncology has become by far the first target for drugs in development including for small molecules and targeted therapies. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), 771 new oncology drugs and vaccines are currently in clinical trials or have been submitted to the FDA for review in US companies (132). Pharmaceutical company investments

remain high and cancer therapies account for more than 30% of all preclinical and phase 1 clinical development (133).

The second most popular indication for gene therapies was monogenic diseases; it was targeted by 10% of all the gene therapy trials. This is not surprising as those diseases are related to one single gene defect and gene therapies are potentially able to correct the gene defect (134). Moreover, as rare conditions, those diseases are expected to reach the market with fewer requirements than common diseases and high prices (135). They are granted (or their developers) special treatment, such as national tax grants; or exemption from "across the board" price cuts or taxes (136, 137) . This makes monogenic diseases an attractive target for manufacturers and investors.

According to the World Health Organization (WHO), cancer and cardiovascular diseases are by far the top leading causes of death worldwide (138, 139). Heart diseases kill over 4 million Europeans every year which constitutes 45% of all deaths (140) , and cancer is responsible of 1.9 million deaths each year in Europe (141). According to a recent study published in 2016, cancer overtook CVD as the leading cause of death in 12 European countries (140). Furthermore, in addition to their clinical burden, chronic diseases have an important economic burden. According to the European Commission 700 billion EUR are spent annually on chronic diseases in the European Union (EU) (142). The numbers of cases of chronic diseases are on the rise and with it the social and economic burden of the diseases, indeed, it has been projected that, by 2020, chronic diseases will account for almost three-quarters of all deaths worldwide (143). Therefore, these disease areas have critical clinical unmet needs and novel curative therapies are needed for these diseases.

These results support our hypothesis on a fast growing number of ATMPs in many disease areas with critical unmet needs. ATMPs may ultimately impact the national health insurance budget in Europe. Moreover 932 studies are currently in very early phase such as pilot studies and were not considered for this research. This will continue to fuel the number of ATMPs in development in the coming years. 65 trials (6.9%) were in phase III suggesting they had a successful phase II with substantial chances to reach the market in the five coming years.

However to our knowledge since it is a new therapy area, there is no success rate per development phase for ATMPs that may allow estimating the potential ones likely to

reach the market. Therefore, we used the same database to evaluate the risk of discontinuation of ATMP trials.

5.6. Rate of discontinuation of ATMP trials

Bringing new drugs to the market is a very expensive process (144); drugs development costs are increasing to near $2 billion for each marketed drug (145). Firms need to do portfolio decisions based primarily on expected net present value. Amongst many factors, trials discontinuation rate is a factor to determine the expected net present value of a therapy and to help the manufacturers to decide about investing in a product portfolio and setting their priorities.

In addition, this information may reduce the feelings of mistrust that can complicate the difficult decision about whether the patient will join a trial (146). The patient may be willing to integrate this information when accepting to enroll in a clinical trial and we believe such information may be useful and should be part of inform consent. At the same time physicians may also be interested to appreciate the risk of clinical trial discontinuation or risk of failure when deciding to act as an investigator for a trial, this can reassure them that they are committing themselves to a trial that can lead to important scientific results and is not riskier than the others. This information may also be part of the mix informing the decision (147).

143 ATMPs clinical trials were withdrawn, terminated or prematurely ended between 1999 and June 2015, and 391 ongoing and 83 completed clinical trials started between 1999 and June 2013. The probability of discontinuation of ATMPs is 23.18%. It is almost the same rate of discontinuation that was evaluated by *Kasenda B et al, 2014*, (107) for drugs in development. Therefore, the development of ATMPs as a class may not be riskier than other therapies. However, the differences between therapeutic class are important and this aggregated discontinuation rate should be considered carefully.

The rate of discontinuation of ATMPs trials targeting cancer is the highest (43%), this rate is considerably higher than the discontinuation rate of cancer trials evaluated by Stensland K et al, 2013 (148). They showed that between 2005 and 2012, the rate of discontinuation of cancer trials in phase 2 and 3 was 11.5%. In cardiology, the rate of discontinuation of ATMPs trials is around 20%, whereas it is 10.9% (149) for cardiology clinical trials between 2000 and 2013. It is unclear why the oncology products experience such a higher risk. It may be that the prices of oncology products are so high

(150, 151) compared to other therapeutic area, thus the incentives to invest in the oncology field is higher. Therefore investors and manufacturers may be open for more risk taking attitude for ATMPs targeting oncology indication as the reward may be more important.

Surprisingly the development phase is not affecting the discontinuation rate. The reason is unclear. It may be related to the lowest number of studies in development in later phases or the largest number of studies completed in earlier phases, or a specificity of ATMPs where discontinuation rate may be independent of development phases? This should be further explored when more products will reach later stage.

The discontinuation rates for commercial and non-commercial sponsors are the same, suggesting that the reason of discontinuation may not be financially driven. One may have anticipated that commercial organizations are more cautious and less risk takers thus having lower risk of discontinuation rates compared to non-commercial organisations. This is not supported by our findings.

5.7. ATMPs and payers

Developing ATMPs is complex process because of technical obstacles and uncertainties. Due to the complexity and specificity of ATMPs, new clinical trial methodologies are expected to be considered similarly to what is discussed for oncology products and orphan drugs (e.g. small sample size, non-randomised trials, single arm trials, surrogate endpoints, integrated protocols, combined phase II/III and adaptive designs) (152). Therefore at time of launch payers may end up with insufficient information to assess the potential value of those products launching. Evidence generation post-launch will likely become unavoidable to address payers' uncertainty. Manufacturers developing such products should bear in mind the need to inform payers early on about their product value and be prepared to collect long term follow up information and consider post-launch studies and eventually coverage with evidence development with or without escrow agreements.

Despite their potential for improving efficacy, ATMPs may encounter substantial hurdles to reach the market if the manufacturer did not prepare appropriately the market access strategy and launch sequence. Currently, the increasing number of highly effective therapies approved in EU (153) is creating an increasing financial pressure on healthcare budgets at a period of recovery after a financial crisis and flattening of Gross

Domestic Product (GDP) growth (154). The payers are facing a challenge to create a balance between ensuring the financial sustainability of the healthcare system and encouraging the innovation and development of new therapies to address the unmet needs. This together with poor preparation of pharmaceutical companies may explain the limited success of the 8 approved ATMPs to secure reimbursement in EU. Alipogene tiparvovec, Glybera®, the first gene therapy, is seeking a price of 53,000 euros/vial equivalent to 1.1 million euros per patient. Although it targets a small population group it will create a substantial financial impact by adding to the numerous orphan drugs reaching the market at high price (155, 156). Glybera® is not reimbursed in EU, and Provenge®, ATMP priced at $ 90,000 per 3 doses in the United States (US) (157) was subject to a very high scrutiny of the evidence provided by the manufacturer to Health Technology Assessment (HTA) agencies. It was denied reimbursement in Europe due to the reasons detailed in Chapter 1. Ultimately, Dendreon, the company manufacturing Provenge® went bankrupt primarily but not only because of the poor pricing and market access strategy (89).

Around 30% of phase III trials are for cancers, this shows that oncology remains the closest to fuel future ATMPs to reach the market . In recent years, cancer drug prices have been skyrocketing and place huge funding dilemmas on health-care systems (158). Cancer therapies cost the EU 124 billion euros each year (159). If ATMPs in development meet the expectations, the manufacturers will be targeting premium prices, and this will create a dramatic impact on payers' budget (160). EU5 Payers are reluctant to pay premium prices with immature data while the benefits they are paying for, are expected to materialize beyond the duration of clinical trials (161).

Resource utilisation prioritization will increasingly be required for the introduction of those new medicines and should be transparent and driven by society preferences (160).

The recent example of sofosbuvir showed how unprepared health authorities are and how inappropriate the payers' decision making criteria are, when having to make a decision on a high value product with a major budget impact. Payers tend to deviate from their own decision making established rules and to operate through exceptional rules and cap the drug class expenditure without considering the overall disease expenditure (20).

This situation is likely to replicate many dozens of times in the coming decade. We foresee multiple ATMPs reaching the market with limited clinical evidence but a potential of very high benefit making it extremely difficult for payers to deny access. The society will exercise a high pressure on politicians in charge of the administration and on policy makers to get access to those products. Given the high additional value they may offer to patients and the society, and the high prices anticipated for these products, they may have a substantial budget impact and pose a challenge for the sustainability of public health insurance in Europe.

In the next chapter, we will evaluate the budget impact of ATMPs if they successfully reach the market.

Chapter 3: ATMPs budget impact assessment

1. Introduction

ATMPs are very promising therapies that aim to address many clinical unmet needs (162); they are expected to cure, halt or slow down the progression of many disabling diseases. The ATMPs pipeline is relatively large with 798 ongoing clinical trials across all phases of development but mainly in early phases and targeting several therapeutic areas. As we have shown in the Chapter 1, pricing and reimbursement (P&R) are major challenges for ATMPs, HTA bodies are scrutinizing the clinical evidence and payers are being reluctant to adopt these therapies due to their high price/high reward profile. Prices claimed by manufacturers for ATMPs can be as high as €1.1million like Glybera's price. P&R decisions are discussed and taken on a national level or even at regional level in some countries like Italy. Every country has a decision framework and decision drivers for reimbursement and price negotiation. Jørgensen and Kefalas (2015)(163) identified the most relevant considerations for ATMPs pricing and reimbursement in the big 5EU (France, Germany, UK, Italy, Spain); the budget impact as well as the incremental clinical benefit are key considerations in all P&R processes, in addition the cost-effectiveness analyses are increasingly applied.

- In France, a new therapy with important improvement in actual benefit (IAB or ASMR I-III) and an estimated budget impact over €20 million per year has to undergo a cost-effectiveness evaluation by the economic commission (CEESP) (164).
- In Germany, P&R decisions are mainly driven by the early benefit assessment and budget impact. The latter is the main health economic evaluation applied in Germany (163).
- Similarly in Italy, the budget impact is a key consideration for innovative advanced therapies in addition to real-world evidence collected through registries (165).
- In Spain, the cost-effectiveness and budget impact evaluations are requested in the dossier but the budget impact is the key driver for P&R negotiations.
- In the UK, NICE applies a value-based assessment based on the clinical effectiveness and cost-effectiveness considerations. The UK has a defined threshold that links the cost per quality-adjusted life year (QALY) to the reimbursed price. The threshold is between £20,000 and £30,000/QALY (166). In an effort to address the discrepancies between cost-effectiveness and budget impact, and to ensure access for novel therapies with maintaining the financial

sustainability of NHS, NICE introduced in March 2017 a budget impact threshold of £20millions per year. Companies developing cost-effective drugs that are expected to have a budget impact equal or higher than £20millions in the first 3 years, will benefit from confidential negotiations with the NHS. These negotiations help avoid delays in patients access to treatments recommended by NICE. A budget impact test is applied for applications starting April 2017 (167).

Budget impact analysis (BIA) is considered part of economic evaluation of a new intervention; it is increasingly gaining importance in the health technology assessment procedures. This analysis aims to estimate the financial consequences of adoption of a new therapy within a specific health care setting (168). The important expected clinical benefit of ATMPs in the different disease areas will rationally be linked to a high price requested by the manufacturer and therefore a high impact on health insurance budgets. The number of published budget impact studies is significantly lower than cost effectiveness studies. Van de Vooren et al. (169) identified through a systematic review 17 BIA publications focusing on European countries. Amongst the publications included in this review, only two BIAs were studying the budget impact of biological treatments and none of these studies was conducted in the CEE region. No studies assessing the expected budget impact of ATMPs have been published so far. There is a need to understand the cost-effectiveness and budget impact of ATMPs to make coverage decisions.

Therefore, the aim of our study was to evaluate ATMPs Drug budget impact (DBI) on Health Insurance (HI). The analysis was conducted in 3 selected diseases: in Alzheimer's Disease (AD) and Parkinson Disease (PD) assuming various efficacy profiles in United Kingdom (UK) setting from National Health Services (NHS) and societal perspectives and heart failure from French payer perspective.

1.1. ATMPs in Parkinson's disease

Parkinson's disease (PD) - one of the most common neurodegenerative disorders - is a progressive disorder characterized by a large number of motor and non-motor degeneration (170) that has an estimated annual cost in Europe of €13.9bn (171). The current pharmacological therapy, Levodopa (L-DOPA) and dopamine agonists are effective for the first years after disease onset. However, L-DOPA has several limitations that appear few years after beginning the treatment: "dopa resistant" motor symptoms e.g. postural abnormalities, speech impairment, freezing episodes, "dopa resistant" non-

motor signs e.g. autonomic dysfunction, mood and cognitive impairment, and/or drug related side effects: psychosis, motor fluctuations, and dyskinesia (172). The development of cell therapies to replace the degenerated neurons started in 1992 by *Lindvall et al* (173). These therapies aimed to transplant fetal Dopamine precursors into the striatum and increase dopamine levels in the basal ganglia. Many researchers worked on developing these cell replacement therapies. DA neuron-like cells have been generated from a variety of adult stem cells such as bone marrow mesenchymal stem cells (BM-MSCs), placenta-derived MSCs, adipose tissue-derived stem cells (ADSCs). Caiazzo et al, 2011, used reprogramming methods to develop DA neurons from somatic cells (174). Nowadays, around 20 clinical trials using cell therapies are ongoing (175): a phase I, open-label, single center, uncontrolled clinical trial (NCT02452723) is conducted by International stem cell corporation (ISCO), to evaluate the safety of ISC-hpNSC (neural stem cells derived from human parthenogenetic stem cells), intracranially transplanted into patients with moderate to severe Parkinson's disease (176) . Another Phase I open label study is conducted to test Human OK99 Allogeneic Stem Cell Transplantation for Patients with Severe Parkinson's Disease.

In addition, many gene therapies are being developed to treat PD; for example, aromatic amino acid decarboxylase (AADC) gene transfer is in Phase I of development. AADC is an enzyme in the brain that converts levodopa into dopamine which the brain can use to improve Parkinson's symptoms. hAADC gene is packaged into a gene transfer vector derived from a common, non-pathogenic virus (AAV2) (NCT01973543) .

1.2. ATMPs in Alzheimer's disease

ATMPs are also being developed to treat AD. AD is a degenerative brain disease that contributes to 60-80% of dementia cases. In 2015, the worldwide federation of Alzheimer associations, Alzheimer's disease International, estimated that 46.8 million people worldwide suffer from AD, with a global cost of US$818 billion (177). Many unmet needs remain in this area, at present (178); no disease modifying therapies are available. Researchers started the investigation on the use of stem cells for treating AD.

Several cell types have been studied in animal models including bone marrow-derived mesenchymal stem cells, adipose-derived stem cells, and neural stem cells. Many beneficial outcomes have been demonstrated like reversal of memory deficits, the

removal or reduction of disease pathologies, and provision of trophic support from donor cells to remaining neuronal circuits (179).

Duncan T and Valenzuela M. 2017 (180), have identified 7 ongoing clinical trials in humans for stem cells targeting AD (NCT01547689, NCT02054208, NCT02600130, NCT02912169, NCT02833792, NCT02672306, NCT02899091). The trials are in early phases of development: phase I, I/II or II.

1.3. ATMPs in heart failure

Heart failure (HF) is a major public health issue that constitutes the leading cause of death worldwide (181). Heart failure patients' number is growing, around 26 million of patients worldwide are suffering from HF (182). Heart failure generally affects older people, it has a poor prognosis, and leads a fivefold increase in the risk of death (183); around 50% of patients die 5 years after diagnosis (184) and 45% of cardiovascular deaths are sudden deaths (185). Many treatments have been developed to cure heart failure, however despite all improvements, 1 in 4 HF patients die within 1 year (186, 187). Hence, the new therapies that can radically treat HF patients and ameliorate its prognosis are important for public health. Currently, a number of cell therapies are in development for myocardiac repair in myocardiac infarction (188-190) and chronic heart failure (191). SCIPIO and CADUCEUS were the first two randomized clinical trials that tested stem cells in end-stage HF adult patients, and showed regarding cell therapy safety and efficacy (192, 193). In the Committee of advanced therapies workshop, Dr Assmus confirmed that: "regenerative therapies have now emerged as a promising novel approach to improve heart function and prevent the development of end-stage heart failure" (120). Different administrations exist: intracoronary, intramyocardial, intravenous, and epicardial. This therapeutic strategy consists on the injection of cells in the site of damage in the heart, these cells stimulates the regeneration of the damaged tissue and possibly the recovery of its function. A systematic review of Jeevanantham V et al, 2012 (194) showed that bone marrow cell (BMC) transplantation can improve the left ventricular function, infarct size, and remodeling and reduce the incidence of death, recurrent myocardial infarction, and stent thrombosis.

Ixmyelocel-T, an investigational autologous expanded multicellular therapy manufactured by Vericel for the treatment of heart failure has received in February 2017 a Fast Track Designation from FDA. A large phase 2B trial was conducted to compare Ixmyelocel-T to placebo in patients with heart failure NYHA class III or IV. The

primary endpoint results showed a 37% reduction in cardiac events compared with placebo (risk ratio 0·63 [95% CI 0·42-0·97]; p=0·0344) (195). Ixmyelocel-T will now be in phase 3. Ixmyelocel-T will also be investigated in other cardiac related conditions and hyperlipidemia.

2. Materials and methods

2.1. Parkinson's disease model

2.1.1. Data sources

Data used as input in the models were identified through extensive literature review. A systematic literature review was conducted in MEDLINE, Google scholar, Embase and the grey literature to identify all economic evaluations for PD therapies in UK.

The search strategy consisted of:

#1	(decision adj1 (tree$ or analy$ or model$)).ti,ab.
#2	(qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab.
#3	(sensitivity analys$s or "willingness to pay" or quality-adjusted life year$ or quality adjusted life or quality of life).ti,ab.
#4	(markov chain$ or monte carlo).mp.
#5	cost$effective$.ti,ab.
#6	cost effective$.ti,ab.
#7	cost*effective$.ti,ab.
#8	utilit$.mp.
#9	(economic adj2 evaluation).tw.
#10	cost benefit analysis.tw.
#11	cost$ utilit$ analys$.tw.
#12	cost benefit analys$.tw.
#13	(eq5d or eq 5d or euroqol).ti,ab.
#14	(hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
#15	(cost or costs or costly or costing$).ti,ab.
#16	(economic$ or price$ or pricing or pharmacoeconomic$).ti,ab.
#17	*Cost-Benefit Analysis/
#18	*Economics, Medical/

#19	*Models, Economic/
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21	#20 AND Parkinson$.ti,ab.

Studies between 2000 and May 2017 were screened. Fifty one articles were included.

To extract model input data, we selected studies conducted in UK. Six studies were selected for this aim.

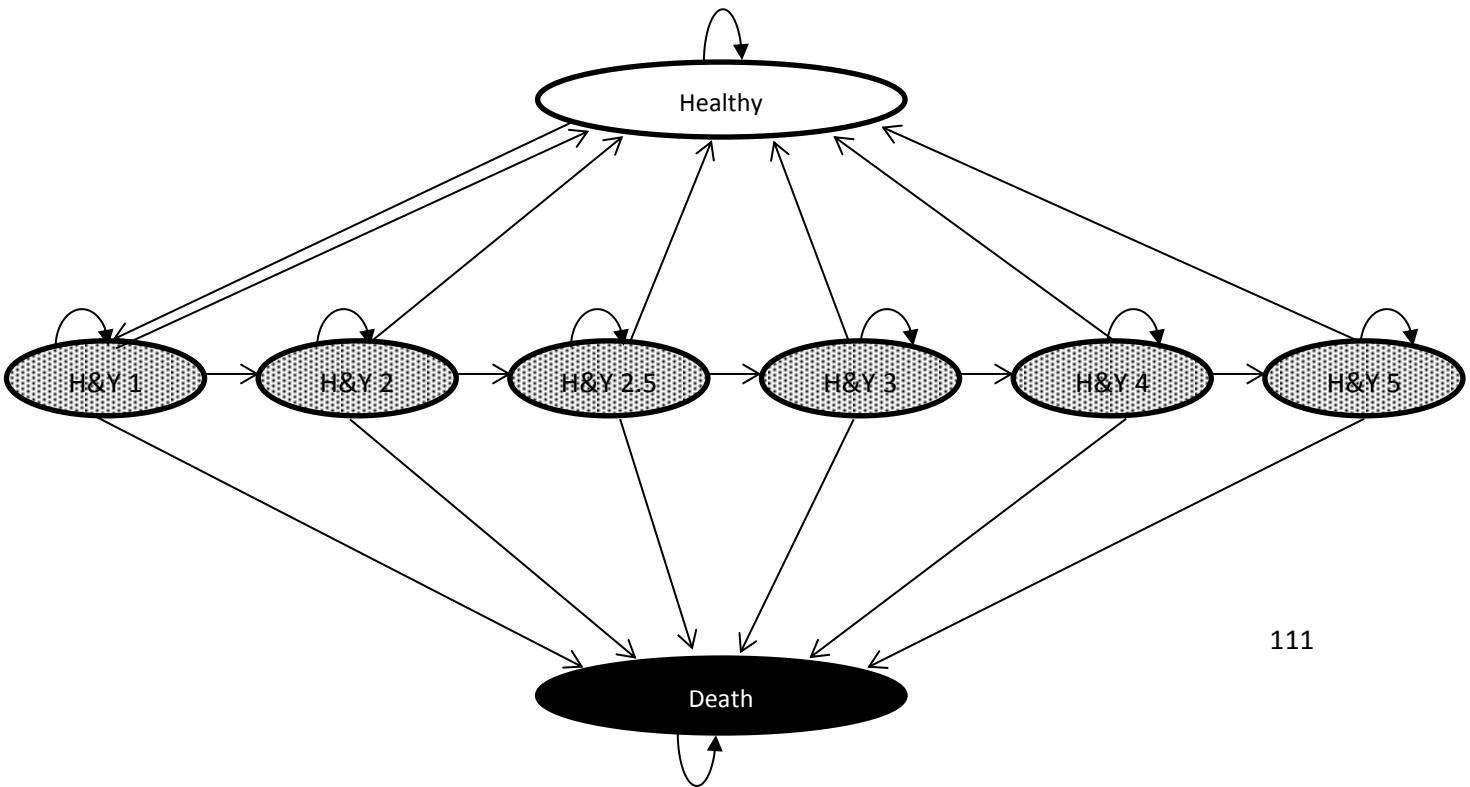
2.1.2. Model description

A Markov model was developed (Figure 22), based on models published by Findley et al, 2005 (196) and Zhao et al 2010. (197). The Markov model was composed of 8 health states: healthy, 6 Hoehn and Yahr (H&Y) stages of PD (H&Y stages 1, 2, 2.5, 3, 4, 5) and death.

H&Y staging is used to establish the severity of PD, stages of disease are classified from 1 to 5 where (198):

- H&Y 1: indicates unilateral disease
- H&Y 2: indicates bilateral without postural instability
- H&Y 2.5: indicates mild bilateral disease with recovery on pull test
- H&Y 3: indicates postural instability
- H&Y 4: indicates considerable disability but ability to walk independently
- H&Y 5: indicates wheelchair-bound or walking only with assistance.

Figure 22. Markov model for Parkinson's disease



The model started with an initial distribution of patients in assigned states derived from a study of Hjelmgren J et al., 2006 (199) :

- H&Y 1 : 34.2%
- H&Y 2 : 31.6%
- H&Y 2.5: 0%
- H&Y 3 : 22.8%
- H&Y 4 : 10.1%
- H&Y 5 : 1.3%

Patients receive the standard of care or an ATMP. The standard of care consisted of traditional levodopa/ Dopa-decarboxylase inhibitor, which is the first-line treatment for PD patients according to the NICE updated guidelines (NICE, July 2017)(200).
The transition between H&Y stages rarely happened in less than one year based on Zhao et al, 2010 (197) study, however to make sure to have a precise estimation, the model was analyzed as cohort simulation with 6-month cycle length, as used in Findley et al analysis (196), corresponding to the usual follow-up duration in PD treatments clinical trials (196, 201, 202), and a time horizon of 10 years which is a period that can reflect the important differences in costs or outcomes between SoC and ATMP.

All analyses were conducted from the United Kingdom (UK) National Health Services (NHS) perspective, the provider of health services, and societal perspective.

2.1.3. Transition probabilities

The model describes the transition of patients through the 6 H&Y health states for 10 years or until death. Death is considered an absorbing state of the model.

Transition probabilities for the standard of care (SoC) were adopted from Zhao et al., 2010 (197) and adjusted in order to have the probabilities for a cycle of 6 months (Table 17). With the standard of care, patients could stay in the same state or the disease could be worsened - they moved to more advanced state- or they could die.

Table 17. Transition probabilities for a 6-month cycle with the SoC for PD

	Healthy	H&Y 1	H&Y 2	H&Y 2.5	H&Y 3	H&Y 4	H&Y 5	Death
Healthy	0	0	0	0	0	0	0	0

H&Y 1	0	0,729	0,271	0	0	0	0	0
H&Y 2	0	0	0,791	0,130	0	0	0	0,079
H&Y 2.5	0	0	0	0,692	0,221	0	0	0,087
H&Y 3	0	0	0	0	0,726	0,166	0	0,108
H&Y 4	0	0	0	0	0	0,672	0,213	0,115
H&Y 5	0	0	0	0	0	0	0,758	0,242
Death	0	0	0	0	0	0	0	1

Transition probabilities after ATMP administration varied depending on the efficacy scenarios. Mortality rates were assumed to be the same with or without ATMP. In this study, the 5 different efficacy scenarios for an ATMP were:

- **Scenario 1:**

100% of patients were cured after the ATMP administration.

Table 18. Transition probabilities (6-month) for ATMP (Scenario 1)

	Healthy	H&Y 1	H&Y 2	H&Y 2.5	H&Y 3	H&Y 4	H&Y 5	Death
Healthy	1	0	0	0	0	0	0	0
H&Y 1	1	0	0	0	0	0	0	0
H&Y 2	0,921	0	0	0	0	0	0	0,079
H&Y 2.5	0,913	0	0	0	0	0	0	0,087
H&Y 3	0,892	0	0	0	0	0	0	0,108
H&Y 4	0,885	0	0	0	0	0	0	0,115
H&Y 5	0,758	0	0	0	0	0	0	0,242
Death	0	0	0	0	0	0	0	1

- **Scenario 2:**

50% of patients were cured after the ATMP administration in the first cycle, the others progressed as with SoC (Table 17).

- **Scenario 3:**

Probability of progression was 50% less than the probability of progression with the SoC in each cycle (Table 19).

Table 19. Transition probabilities (6-month) for ATMP (Scenario 3)

	Healthy	H&Y 1	H&Y 2	H&Y 2.5	H&Y 3	H&Y 4	H&Y 5	Death
Healthy	1,000	0	0	0	0	0	0	0
H&Y 1	0	0,865	0,135	0	0	0	0	0
H&Y 2	0	0	0,856	0,065	0	0	0	0,079
H&Y 2.5	0	0	0	0,802	0,110	0	0	0,087
H&Y 3	0	0	0	0	0,809	0,083	0	0,108
H&Y 4	0	0	0	0	0	0,779	0,107	0,115
H&Y 5	0	0	0	0	0	0	0,758	0,242
Death	0	0	0	0	0	0	0	1

- **Scenario 4:**

Probability of progression was 67% less than the probability of progression with the SoC in each cycle (Table 20).

Table 20. Transition probabilities (6-month) for ATMP (Scenario 4)

	Healthy	H&Y 1	H&Y 2	H&Y 2.5	H&Y 3	H&Y 4	H&Y 5	Death
Healthy	1	0	0	0	0	0	0	0
H&Y 1	0	0,910	0,090	0	0	0	0	0
H&Y 2	0	0	0,878	0,043	0	0	0	0,079
H&Y 2.5	0	0	0	0,839	0,074	0	0	0,087
H&Y 3	0	0	0	0	0,837	0,055	0	0,108
H&Y 4	0	0	0	0	0	0,814	0,071	0,115
H&Y 5	0	0	0	0	0	0	0,758	0,242
Death	0	0	0	0	0	0	0	1

- **Scenario 5:**

The ATMP could stop the progression of the disease; patients were stable in the same health state (Table 21).

Table 21. Transition probabilities (6-month) for ATMP (Scenario 5)

	Healthy	H&Y 1	H&Y 2	H&Y 2.5	H&Y 3	H&Y 4	H&Y 5	Death
Healthy	1	0	0	0	0	0	0	0
H&Y 1	0	1	0	0	0	0	0	0
H&Y 2	0	0	0,921	0	0	0	0	0,079
H&Y 2.5	0	0	0	0,913	0	0	0	0,087
H&Y 3	0	0	0	0	0,892	0	0	0,108
H&Y 4	0	0	0	0	0	0,885	0	0,115
H&Y 5	0	0	0	0	0	0	0,758	0,242
Death	0	0	0	0	0	0	0	1

2.1.4. PD model input

Utilities and Costs of each health state were obtained from published source (Findley et al, 2005) (196), presented in Table 22. The 2003 costs from the article were adjusted to 2016 cost levels based on the UK Consumer Price Index (CPI) for Health.

The mean societal costs per patient were composed of the 3 following costs:

1) NHS direct cost: Primary care including: drugs, GP visits, home visits by other health professionals, and secondary care including: hospital in- and outpatient care,
2) Social services costs: Home help/support, formal home care, meals on wheels, nursing homes, sitting services, day centers, miscellaneous
3) Private PD-related expenditures: Private residential/nursing home costs, home help services, special equipment, travel, miscellaneous.

Table 22. Costs and utilities for PD model (196)

	Healthy	H&Y 1	H&Y 2	H&Y 2.5	H&Y 3	H&Y 4	H&Y 5	Death
Mean NHS costs £/6months (SD)	0	1158 (1357)	1191 (1057)	1656**	2148 (3798)	2986 (3477)	3366 (5652)	0
Mean total societal costs £/6months (SD)	0	2336 (3409)	2411 (3146)	3538**	4839 (6415)	7883 (6550)	14097 (11217)	0
Mean utility* EQ-5D per health state (SD)	0.96 (0.13)	0.96 (0.13)	0.65 (0.34)	0.56 (0.29)	0.26 (0.32)	0.19 (0.62)	-0.21 (0.17)	0

* Mean utility EQ-5D per health state independent of treatment, ** Standard deviation not reported, SD: Standard deviation

2.1.5. Discount rates

Discount rates for cost and QALYs were 3.5% per year in line with NICE methodological guidance (203).

2.1.6. Cost-effectiveness analysis

Hypothetical cohorts of 10,000 patients were created for each scenario (scenarios described above) and then allowed to flow through the course of disease from entry.

In all scenarios, we assumed that ATMP was administered once in the first cycle and then patients that were not cured continued to receive SoC. One ATMP administration was supposed to be sufficient to achieve the scenario outcome. ATMP price was added on top of SoC costs only at the first cycle.

The discounted QALYs gained, the discounted costs, the incremental utility and incremental cost were calculated.

Scenarios were tested to identify ATMPs price assuming an ICER threshold of 30,000£/QALY gained (166).

ATMP price was defined in each scenario as the maximum price to reach the ICER threshold.

$$\text{ICER} = \frac{\text{Cost}(ATMP) - \text{Cost(SoC)}}{\text{E(ATMP)} - \text{E(SoC)}}$$

2.1.7. Budget impact

The BIA predicted the impact of ATMP on the budget of national payers over a 5-year timeframe. It compares a “world with ATMP” to a “world without ATMP”.
The analysis was conducted in compliance with the principles of good practice for BIA from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (204). The perspective of analysis was that of a third party payer. Undiscounted costs were used for the budget impact calculation.

The size of the patient population that will receive the ATMP in the first year was the prevalence of PD in UK and the incidence of PD in UK for the 4 following years. The prevalence of PD in UK was 6-11 people per 6,000 (205) of the general population,

therefore 119,351 patients (considering the UK population in 2016 was 65,100,477). And the incidence in UK was 15.8/10,000 (206).

2.1.8. Sensitivity analysis

Deterministic sensitivity analysis was performed. Specifically, tornado graphs were built to explore the sensitivity of results to a change of ±10% in different parameter assumptions: utilities, NHS costs of the disease stages. Efficacy assumptions and transition probabilities were tested in the different scenarios used in the model.

2.2. Alzheimer's disease model

2.2.1. Data sources

Data used as input in the models were identified through extensive literature review. A systematic literature review was conducted in MEDLINE, Google scholar, Embase and the grey literature to identify all economic evaluations for AD therapies in UK.

The search strategy consisted of:

#1	(decision adj1 (tree$ or analy$ or model$)).ti,ab.
#2	(qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab.
#3	(sensitivity analys$s or "willingness to pay" or quality-adjusted life year$ or quality adjusted life or quality of life).ti,ab.
#4	(markov chain$ or monte carlo).mp.
#5	cost$effective$.ti,ab.
#6	cost effective$.ti,ab.
#7	cost*effective$.ti,ab.
#8	utilit$.mp.
#9	(economic adj2 evaluation).tw.
#10	cost benefit analysis.tw.
#11	cost$ utilit$ analys$.tw.
#12	cost benefit analys$.tw.
#13	(eq5d or eq 5d or euroqol).ti,ab.
#14	(hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
#15	(cost or costs or costly or costing$).ti,ab.
#16	(economic$ or price$ or pricing or pharmacoeconomic$).ti,ab.

#17	*Cost-Benefit Analysis/
#18	*Economics, Medical/
#19	*Models, Economic/
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21	#20 AND Alzheimer$.ti,ab.

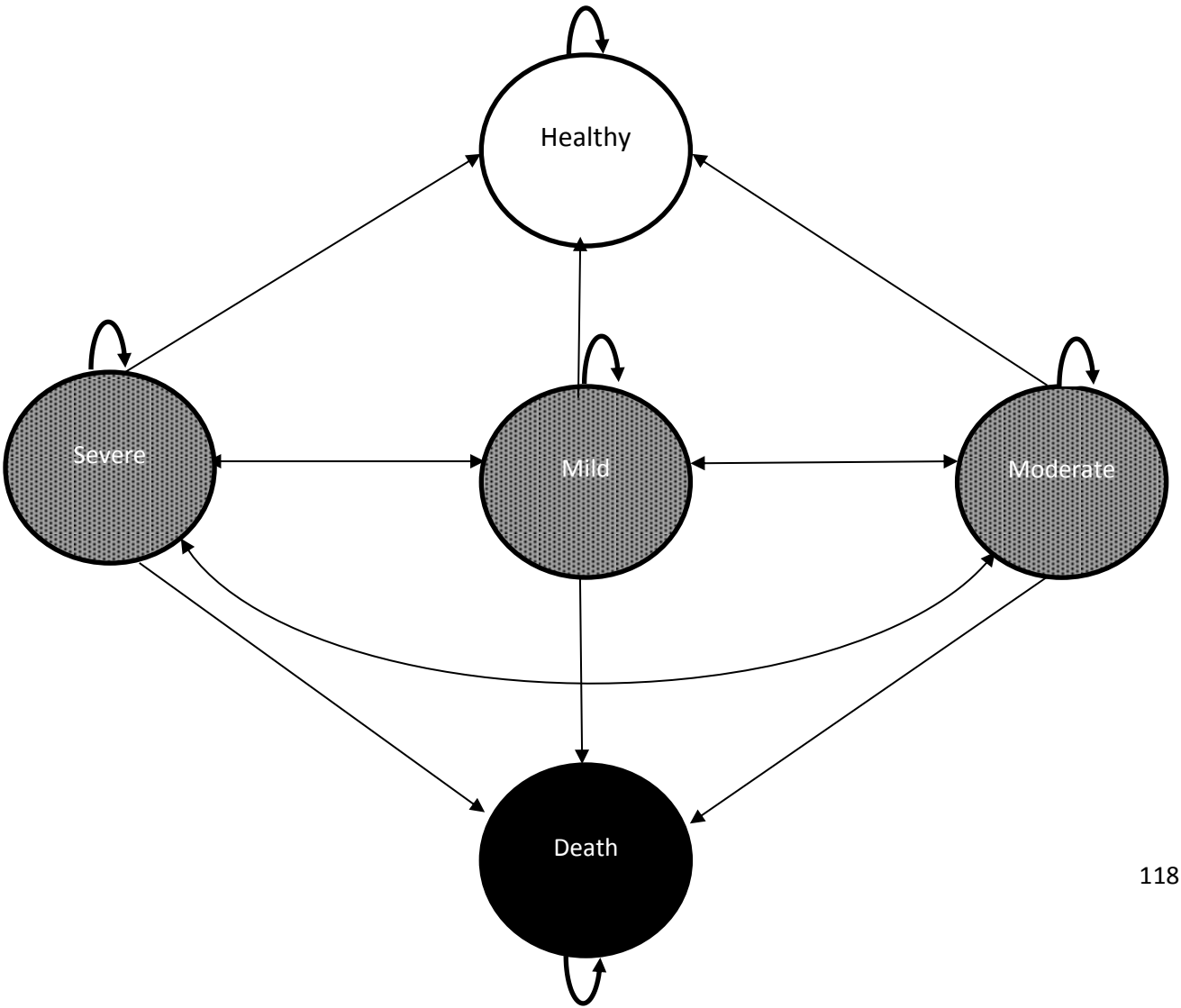
Studies between 2000 and May 2017 were screened. Eighty articles were included.

To extract model input data, we selected studies conducted in UK. Ten studies were selected for this aim.

2.2.2. AD model description

A Markov model was developed (Figure 23), it was adopted from the model proposed by Green C et al, 2011 (207) for Alzheimer progression. The Markov model was composed of 5 health states: healthy, moderate, mild, severe and death.

Figure 23. Markov model for Alzheimer's disease



The disease severity was defined using Mini-Mental State examination (MMSE) criteria consistent with UK clinical guidelines, MMSE is one of the different methods used to assess the severity of Alzheimer's disease, it denotes the severity of cognitive impairment (208):

- 'Mild AD severity' : MMSE 21−26 points;
- 'Moderate AD severity': MMSE 15−20 points;
- 'Moderately severe/severe AD severity': MMSE <15 points.

Patients were initially distributed between health states based on the cohort used in GERAS study (209) :

- Mild AD: 38%
- Moderate AD: 34%
- Moderately severe/severe AD: 28%

The model time horizon was 5 years and cycle length was 1 month. A 5-year time horizon has been used in the Alzheimer treatments economic models submitted to NICE. The evidence suggests that time from diagnosis to death for AD patients is about 5-20 years (210).

Patients were treated by either the standard of care: acetylcholinesterase inhibitor and/or memantine or the ATMP (NICE guidance, 2011 (208)).

All analyses were conducted from the United Kingdom (UK) National Health Services (NHS) perspective, the provider of health services, and societal perspective.

2.2.3. Transition probabilities

The Markov model used transitions of patient cohorts, with estimated transition probabilities based on data published by from Bloudek et al, 2011 (211).

Table 23. Transition probabilities for a 1-month cycle with the SoC for AD

From\To	Healthy	Mild	Moderate	Severe	Dead
Healthy	1	0	0	0	0
Mild	0	0,996	0,003	0	0,001
Moderate	0	0,032	0,931	0,008	0,029
Severe	0	0	0,005	0,865	0,130
Dead	0	0	0	0	1

Transition probabilities after ATMP administration varied depending on the scenarios. Mortality rates were assumed to be the same with or without ATMP. In this study, the same 5 efficacy scenarios for ATMP used in PD were tested:

- **Scenario 1:**

100% of patients were cured after the ATMP administration (**Table 24**).

Table 24. Transition probabilities (1-month) for ATMP (Scenario 1)

	Healthy	**Mild**	**Moderate**	**Severe**	**Dead**
Healthy	1	0	0	0	0
Mild	0,999	0	0	0	0,001
Moderate	0,971	0	0	0	0,029
Severe	0,870	0	0	0	0,130
Dead	0	0	0	0	1,000

- **Scenario 2:**

50% of patients were cured after the ATMP administration in the first cycle, the others progressed as with SoC (**Table 23**).

- **Scenario 3:**

Probability of progression was 50% less than the probability of progression with the SoC in each cycle

Table 25 : Transition probabilities (1-month) for ATMP (Scenario 3)

From\To	**Healthy**	**Mild**	**Moderate**	**Severe**	**Dead**
Healthy	1,000	0,000	0,000	0,000	0,000
Mild	0,000	0,997	0,001	0,000	0,001
Moderate	0,000	0,032	0,935	0,004	0,029
Severe	0,000	0,000	0,005	0,865	0,130
Dead	0,000	0,000	0,000	0,000	1,000

- **Scenario 4:**

Probability of progression was 67% less than the probability of progression with the SoC in each cycle (Table 26).

Table 26. Transition probabilities (1-month) for ATMP (Scenario 4)

	Healthy	Mild	Moderate	Severe	Dead
Healthy	1	0	0	0	0
Mild	0	0,998	0,001	0	0,001
Moderate	0	0,032	0,937	0,003	0,029
Severe	0	0	0,005	0,865	0,130
Dead	0	0	0	0	1

- **Scenario 5:**

The ATMP could stop the progression of the disease; patients were stable in the same health state (Table 27).

Table 27. Transition probabilities (1-month) for ATMP (Scenario 5)

	Healthy	Mild	Moderate	Severe	Dead
Healthy	1	0	0	0	0
Mild	0	0,999	0	0	0,001
Moderate	0	0,032	0,939	0	0,029
Severe	0	0	0,005	0,865	0,130
Dead	0	0	0	0	1

2.2.4. AD model input

Costs and utilities were extracted from *Wimo et al, 2013* (209) study and presented in Table 28. Baseline cost data were calculated from resource use information obtained from the Resource Utilization in Dementia (RUD) instrument and from additional data collected from caregivers on treatments, financial assistance, out-of-pocket expenses, and neuropsychological assessments.

The 2010 Monthly costs were adjusted to 2016 cost levels based on the UK Consumer Price Index (CPI) for Health.

The NHS costs included:

- Patient health care costs: costs of medications (AD medications, antipsychotic/hypnotic medication, medications for co-morbidities), nights in hospital, emergency room visits, and outpatient visits;

- Caregiver health care costs: costs of medications for caregiver medical conditions, caregiver nights in hospital, emergency room visits, and outpatient visits.

The societal costs included the NHS costs in addition to:

- Patient social care costs: costs of patient living accommodation, community care services, structural adaptations to the patient's living accommodation, consumables, and financial support received;
- Caregiver informal care costs: costs of caregiver time and of the caregiver missing work.

Health related quality of life (HRQoL) was evaluated using the European Quality of Life-5 Dimensions (EQ-5D). EQ-5D is an instrument that helps to assess overall health status. In GERAS study, the proxy was completed by the caregivers.

Table 28. Costs and utilities for AD model

	Mild AD	Moderate AD	Severe AD
EQ-5D index (UK) (95% CI)	0.68 (0.65 ; 0.72)	0.65 (0.61 ; 0.69)	0.48 (0.43; 0.53)
NHS costs per patient (UK, 2016)	320£	274£	295£
Societal costs per patient (UK, 2016)	1621£	1836£	2785£

EQ-5D : European Quality of Life-5 Dimensions, NHS: National Health Services

2.2.5. Discount rates

Discount rates for cost and quality adjusted life years (QALYs) were 3.5% per year in line with NICE methodological guidance (203).

2.2.6. Cost-effectiveness analysis

Hypothetical cohorts of 10,000 patients were created for each scenario and then allowed to flow through the course of disease from entry.

Similarly, we assumed that ATMP was administered once in the first cycle and then patients that were not cured continued to receive SoC. One ATMP administration was supposed to be sufficient to achieve the scenario outcome. ATMP price was added on top of SoC costs only at the first cycle.

The discounted QALYs gained, the discounted costs, the incremental utility and incremental cost were calculated.

ATMP price was defined in each scenario as the maximum price to reach the ICER threshold. The same ICER threshold of 30,000£/QALY gained was adopted for AD (166).

$$\text{ICER} = \frac{\text{Cost}(ATMP) - \text{Cost(SoC)}}{\text{E(ATMP)} - \text{E(SoC)}}$$

2.2.7. Budget impact

The budget impact analysis method was the same as PD. The analysis was conducted in compliance with the principles of good practice for BIA from the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (204). The perspective of analysis was that of a third party payer.

Undiscounted costs were used for the budget impact calculation.

Inputs required for the budget impact analysis include prevalence and incidence of AD in UK. AD constituted 62% of Dementia cases (212). The AD estimated prevalence in 2015 was 527,000 (212) and the AD incidence was 129,952 (213).

2.2.8. Sensitivity analysis

Deterministic sensitivity analyses were implemented. Tornado graphs were built to explore the sensitivity of results to a change by ±10% of different parameter assumptions: utilities, NHS costs of the different stages of AD.

2.3. Heart Failure Markov model

2.3.1. Data sources

Like the two previous models, data used as input in the models were identified through extensive literature review conducted in MEDLINE, Google scholar, Embase and the grey literature to identify all economic evaluations for HF therapies in France.

The search strategy consisted of:

#1	(decision adj1 (tree$ or analy$ or model$)).ti,ab.
#2	(qol or qoly or qolys or hrqol or qaly or qalys or qale or qales).ti,ab.
#3	(sensitivity analys$s or "willingness to pay" or quality-adjusted life year$ or quality

	adjusted life or quality of life).ti,ab.
#4	(markov chain$ or monte carlo).mp.
#5	cost$effective$.ti,ab.
#6	cost effective$.ti,ab.
#7	cost*effective$.ti,ab.
#8	utilit$.mp.
#9	(economic adj2 evaluation).tw.
#10	cost benefit analysis.tw.
#11	cost$ utilit$ analys$.tw.
#12	cost benefit analys$.tw.
#13	(eq5d or eq 5d or euroqol).ti,ab.
#14	(hui or hui2 or hui 2 or hui3 or hui 3).ti,ab.
#15	(cost or costs or costly or costing$).ti,ab.
#16	(economic$ or price$ or pricing or pharmacoeconomic$).ti,ab.
#17	*Cost-Benefit Analysis/
#18	*Economics, Medical/
#19	*Models, Economic/
#20	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21	#20 AND “heart failure”.ti,ab.

Studies between 2000 and May 2017 were screened. One hundred three articles were included. To extract model input data, we selected studies conducted in France. Costs and utilities per the New York Heart Association (NYHA) class were searched. When no French data was available, we looked for data in other European countries like UK.

2.3.2. Model description

A third Markov model was developed for heart failure to compare ATMP to the standard of care and identify the ATMP budget impact. The model was a six-state Markov model adopted from Ford E et al, 2012 (214), based on the New York Heart Association (NYHA) classification system: healthy, NYHA I, NYHA II, NYHA III, NYHA IV, and death. NYHA is a functional classification based on severity of symptoms and physical activity (HAS guidelines (215)):

- NYHA I: no limitation of physical activity. Ordinary physical activity does not cause undue breathlessness, fatigue or palpitations.
- NYHA II: slight limitation of physical activity. Ordinary at rest, but ordinary physical activity results in undue breathlessness, fatigue or palpitations.
- NYHA III: marked limitation of physical activity.
- NYHA IV: unable to carry on physical activity without discomfort. Symptoms can be present at rest.

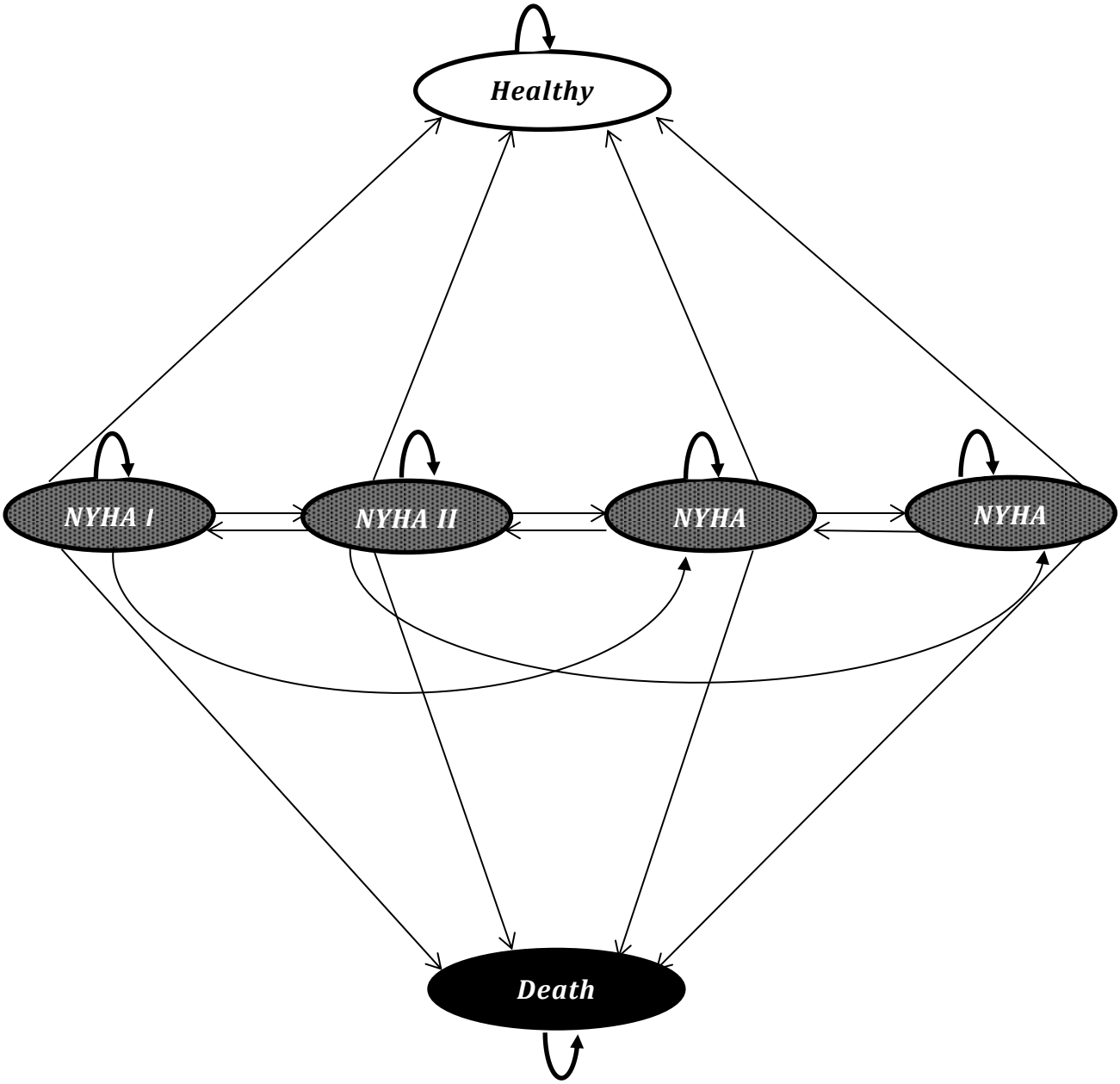
A simulated cohort of 10,000 patients entered the model with an initial distribution between the NYHA states adopted from SENIORS trial (216):

- NYHA I: 2.7%
- NYHA II: 56.3¨%
- NYHA III: 38.7%
- NYHA IV: 2.3%

Heart failure is associated with a poor prognosis with almost half of patients dying within 5 years of diagnosis (217). Therefore, Patients progress through the model in 1 month cycles for a duration of 5 years with a probability of transition between states detailed in the next section. Patients receive the standard of care in HF or the ATMP. The SoC is ACE inhibitor with or without beta-blockers.

The evaluation took a French health insurance perspective.

Figure 24. Markov model for heart failure



2.3.3. Transition probabilities

One-month transition probabilities for cohort patients receiving standard of care between NYHA classes were extracted from published sources (214, 216, 218, 219). After 1 month cycle, patients receiving SoC could either be in the same state or progress to a better or worse stage of the disease (Table 29). Mortality rates were incorporated to the transition probabilities. Mortality with NYHA classes I, II, and III were extracted from Providência R, et al, 2016 (220) and NYHA IV from Muntwyler J et al, 2002 (221).

We assumed that the mortality rates were the same with SoC and ATMP.

Table 29. Transition probabilities with SoC in HF

To From	Healthy	NYHA I	NYHA II	NYHA III	NYHA IV	Death
Healthy	1,000	0,000	0,000	0,000	0,000	0,000
NYHA I	0,000	0,975	0,019	0,004	0,000	0,002
NYHA II	0,000	0,008	0,972	0,010	0,001	0,010
NYHA III	0,000	0,000	0,034	0,950	0,006	0,010
NYHA IV	0,000	0,000	0,034	0,054	0,901	0,011
Death	0,000	0,000	0,000	0,000	0,000	1,000

- **Scenario 1:**

100% of patients were cured after the ATMP administration (Table 30).

Table 30. Transition probabilities (1-month) for ATMP (Scenario 1)

To From	Healthy	NYHA I	NYHA II	NYHA III	NYHA IV	Death
Healthy	1,000	0,000	0,000	0,000	0,000	0,000
NYHA I	0,998	0,000	0,000	0,000	0,000	0,002
NYHA II	0,991	0,000	0,000	0,000	0,000	0,010
NYHA III	0,990	0,000	0,000	0,000	0,000	0,010
NYHA IV	0,989	0,000	0,000	0,000	0,000	0,011
Death	0,000	0,000	0,000	0,000	0,000	1,000

- **Scenario 2:**

50% of patients were cured after the ATMP administration in the first cycle, the others progressed as with SoC (Table 29).

- **Scenario 3:**

Probability of progression was 50% less than the probability of progression with the SoC in each cycle (**Table 31**).

Table 31. Transition probabilities (1-month) for ATMP (Scenario 3)

To From	Healthy	NYHA I	NYHA II	NYHA III	NYHA IV	Death
Healthy	1,000	0,000	0,000	0,000	0,000	0,000
NYHA I	0,000	0,985	0,009	0,004	0,000	0,002
NYHA II	0,000	0,008	0,977	0,005	0,001	0,010
NYHA III	0,000	0,000	0,034	0,953	0,003	0,010
NYHA IV	0,000	0,000	0,034	0,054	0,901	0,011
Death	0,000	0,000	0,000	0,000	0,000	1,000

- **Scenario 4:**

Probability of progression was 67% less than the probability of progression with the SoC in each cycle (Table 32).

Table 32. Transition probabilities (1-month) for ATMP (Scenario 4)

To From	Healthy	NYHA I	NYHA II	NYHA III	NYHA IV	Death
Healthy	1,000	0,000	0,000	0,000	0,000	0,000
NYHA I	0,000	0,991	0,006	0,001	0,000	0,002
NYHA II	0,000	0,008	0,979	0,003	0,000	0,010
NYHA III	0,000	0,000	0,034	0,954	0,002	0,010
NYHA IV	0,000	0,000	0,034	0,054	0,901	0,011
Death	0,000	0,000	0,000	0,000	0,000	1,000

- **Scenario 5:**

The ATMP could stop the progression of the disease; patients were stable in the same health state (Table 33).

Table 33. Transition probabilities (1-month) for ATMP (Scenario 5)

To From	Healthy	NYHA I	NYHA II	NYHA III	NYHA IV	Death
Healthy	1,000	0	0	0,000	0,000	0,000

NYHA I	0	0,975	0.019	0,004	0,000	0,002
NYHA II	0	0.008	0,991	0,010	0,001	0,010
NYHA III	0	0	0,034	0,950	0,006	0,010
NYHA IV	0	0	0,034	0,054	0,901	0,011
Death	0	0	0,000	0,000	0,000	1,000

2.3.4. HF model input

Each state except death was associated with a specific cost and utility (Table 34). Costs and utility sources were identified from the literature review. We were interested by costs and utilities presented by NYHA class in France. No recent costs data per NYHA class was found, therefore costs were extracted from the study of *Berry C et al* (222) and adjusted using the inflation rate (223). Total Costs included direct and indirect costs:

- Direct costs: Hospitalization, Investigation, Drug therapy , Ambulatory care, Heart transplantation/ CABG
- Indirect costs: Loss of income, Carer support, Welfare support, Ambulance transport, Nursing homes

Due to the lack of available data on utilities per NYHA class in France, European utilities data was extracted from Calvert M et al. 2005 based on CARE-HF trial that enrolled patients from 12 European centers.

Table 34. Costs and utilities input for heart failure model

	NYHA I	NYHA II	NYHA III	NYHA IV
Utilities (Range) **(224)**	0.815 (0.781 - 0.850)	0.720 (0.693 - 0.749)	0.590 (0.551 -0.629)	0.508 (0.412- 0.605)
Costs (€) per month **(222)**	88,42	88,42	339,67	680,17

2.3.5. Discount rates

Discount rates for cost and quality adjusted life years (QALYs) were 4% per in line with current recommendations for the French setting in order to adjust for costs and benefits being incurred at different time points throughout the simulation (225).

2.3.6. Cost-effectiveness analysis

Hypothetical cohorts of 10,000 patients were created for each scenario and then allowed to flow through the course of disease from entry. Similarly, we assumed that ATMP was administered once in the first cycle and then patients that were not cured continued to receive SoC. One ATMP administration was supposed to be sufficient to achieve the scenario outcome. In France, there is no threshold value for cost-effectiveness analysis (226), the hypothetical ICER threshold of 50,000€/QALY gained was adopted for HF (164).

ATMP price was defined in each scenario as the maximum price to reach the ICER threshold. ATMP price was added on top of SoC costs only at the first cycle.

$$\text{ICER} = \frac{\text{Cost}(ATMP) - \text{Cost}(\text{SoC})}{\text{E}(\text{ATMP}) - \text{E}(\text{SoC})}$$

2.3.7. Budget impact

The budget impact analysis method was the same as PD and AD. The analysis was conducted in compliance with the principles of good practice for BIA from ISPOR (204). The perspective of analysis was that of a third party payer. Undiscounted costs were used for budget impact analysis.

Inputs required for the budget impact analysis include prevalence and incidence of HF in France. The HF estimated rate of prevalence was 2.3% in France (227) and the HF incidence in 2014 was about 130,000 new cases every year (203.1/100,000) (228).

2.3.8. Sensitivity analysis

Deterministic sensitivity analyses were implemented. Specifically, tornado graphs were built to explore the sensitivity of results to a change in different parameter assumptions: utilities and NHS costs for the different stages of the disease. This provided a statistical distribution, for the key results, including incremental cost effectiveness ratio, NHS costs, and incremental QALY.

3. Results

3.1. Parkinson's disease results

3.1.1. Cost-effectiveness results and ATMP price

The costs, QALYs, and incremental cost-effectiveness ratio of ATMP in PD were shown in Table 35. In PD, the average discounted QALY per patient for the standard of care alone was 1.73 and it was 7.60, 4.93, 2.45, 2.80 and 3.89 respectively for the scenarios 1 to 5 with ATMP. This corresponds to an increase of 339%, 185%, 42%, 62%, and 125% respectively. Societal and NHS costs were increased in the 5 scenarios compared to the standard of care alone. ATMP cost varied between £190,312 (Scenario 1) and £21,501 (Scenario 3) depending on the assumed efficacy.

In the scenario 1 where ATMP was able to cure all the patients (efficacy 100%), its price was £190,312. If the efficacy was 50% (scenario 2), the ATMP price was £102,991. The price of the ATMP that stopped the disease progression but did not cure the diseases was £63,748. ATMP that slowed down the disease progression had lower prices: £21,501 (scenario 3) and £31,850 (scenario 4).

Table 35. Parkinson disease model results

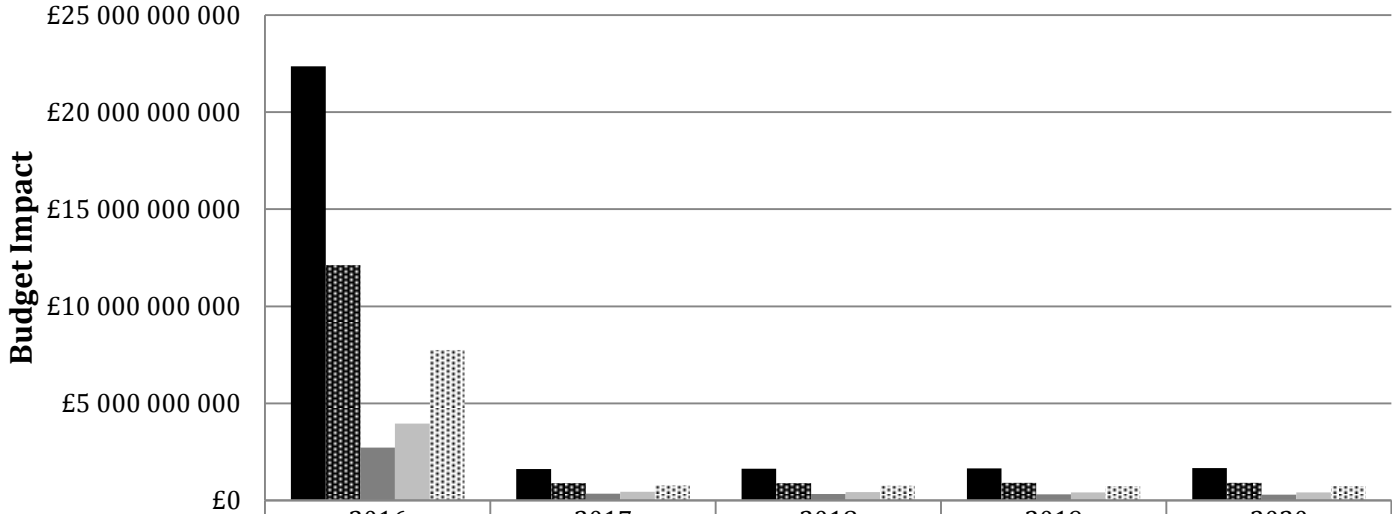
	Standard of care	ATMP				
		Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Total cost (NHS) per patient	£14,319	£190,312	£110,150	£35,736	£46,173	£78,893
Total cost (Societal) per patient	£37,493	£190,312	£121,737	£55,443	£64,928	£96,571
QALYs	1.73	7.60	4.93	2.45	2.80	3.89
ICER (NHS)		£30,000/ QALY	£30,000/ QALY	£30,000/ QALY	£30,000/ QALY	£30,000/ QALY
ICER (societal)		26,050/ QALY	£26,373/ QALY	£25,142/ QALY	£25,838/ QALY	£27,447/ QALY
ATMP price per patient		£190,312	£102,991	£21,501	£31,850	£63,748

QALY: Quality Adjusted Life Years
ICER: Incremental Cost Effectiveness Ratio

3.1.2. Budget impact in PD

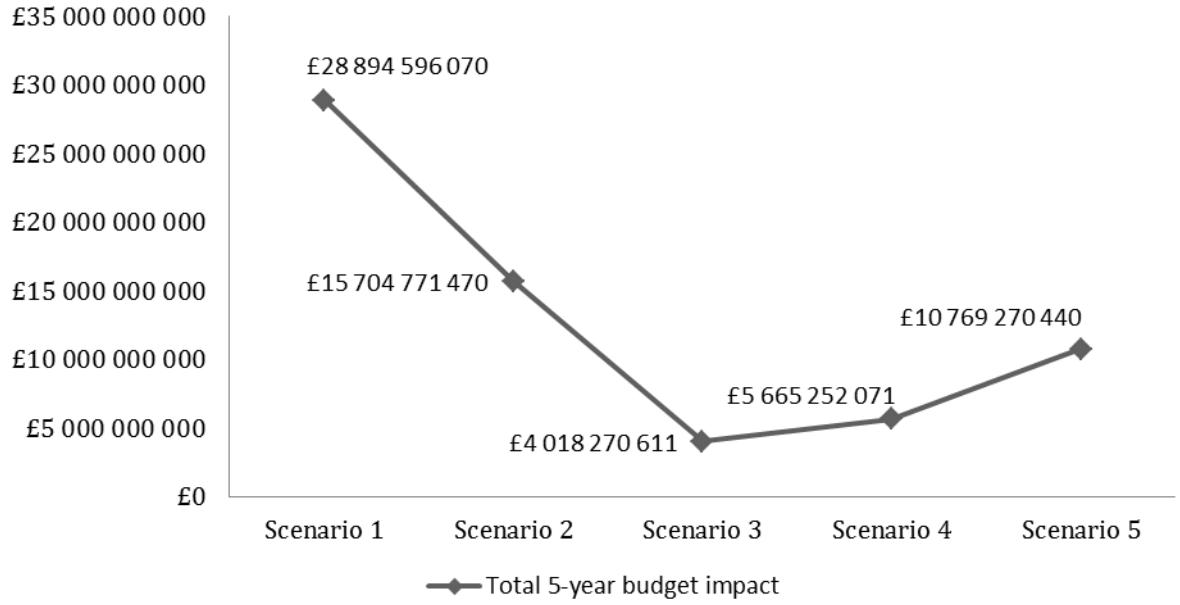
The budget impact calculated based on the number of prevalent and incident cases is presented in for the 5 scenarios in PD in Figure 25. The 5-year total budget impact varied between £29bn and £4bn (Figure 26) . The 5-year total budget impact of an ATMP that cured all patients was £29bn; £22bn in the first year and then decreased to £1.6bn every year. In scenario 2, 5-year total budget impact was around £16bn; £12bn in the first year and around £0.9bn every year. In scenario 3, 5-year total budget impact was £4bn; £2.7bn in the first year and around £0.3bn in the following 4 years. In scenario 4, the 5-year budget impact was £5.6bn: £3.9bn in the first year and £0.4bn every year. In scenario 5, the 5-year total budget impact was £10bn: £7bn in the first year and £0.7bn in the 4 following years.

Figure 25. Annual budget impact of ATMP in Parkinson disease



	2016	2017	2018	2019	2020
Scenario 1	£22 355 303 184	£1 609 382 982	£1 625 691 901	£1 643 399 299	£1 660 818 704
Scenario 2	£12 112 765 694	£885 281 325	£893 435 784	£902 289 483	£910 999 185
Scenario 3	£2 719 634 722	£350 991 553	£331 353 921	£314 915 696	£301 374 718
Scenario 4	£3 951 657 933	£452 957 445	£433 976 247	£419 132 094	£407 528 352
Scenario 5	£7 752 489 193	£772 596 503	£756 045 802	£746 427 585	£741 711 357

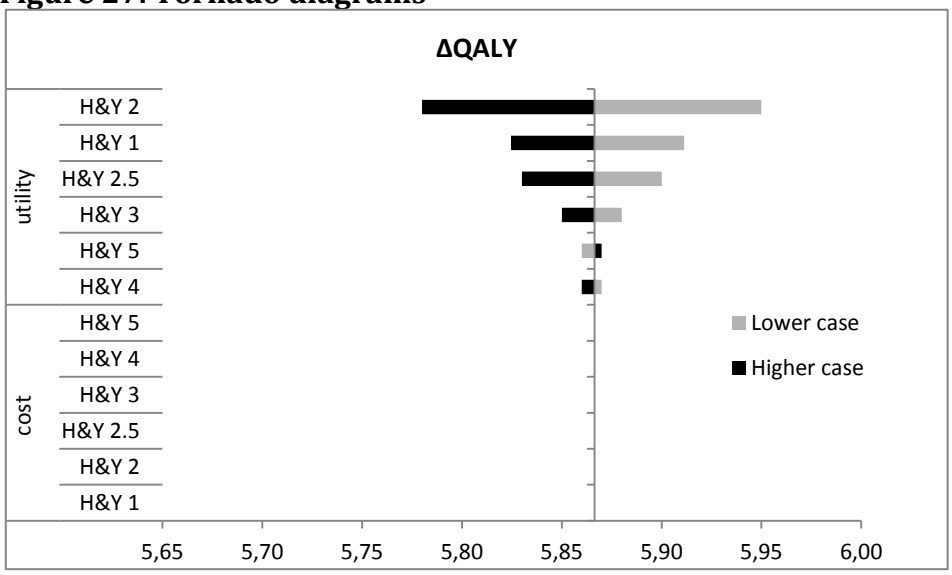
Figure 26. 5-year budget impact in Parkinson disease per scenario

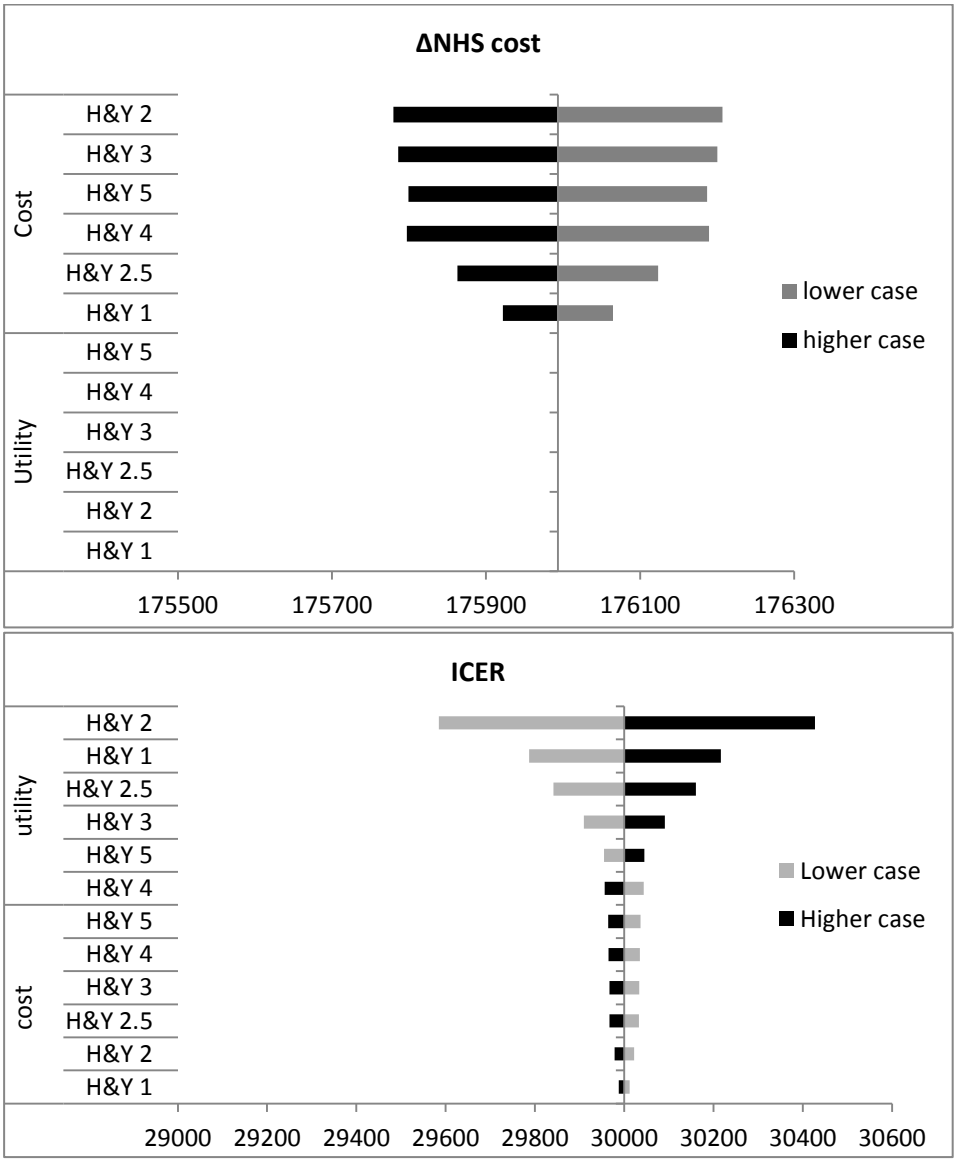


3.1.3. Sensitivity analysis

The sensitivity analysis showed that the model is highly sensitive to the utility of the H&Y 2 PD stage. A 10% increase in the utility of the H&Y2 stage led to an ICER increase from £30,000/QALY to £30,427/QALY (1.4% increase). Figure 27 shows the tornado diagrams of the sensitivity analysis of the PD model.

Figure 27. Tornado diagrams





3.2. Alzheimer's disease results

3.2.1. Cost-effectiveness results and ATMP price

The costs, QALYs, and cost-effectiveness of ATMP in AD were shown in

Table **36** . In AD, the average discounted QALY for the standard of care alone was 1.83, and the average discounted QALY for ATMP was 4.37, 3.15, 1.87, 2.04 and 1.91 respectively for the scenarios 1 to 5. Societal and NHS costs were increased in the 5 scenarios compared to the standard of care administered alone.

The price of ATMP varied between £86,585 (scenario 1) and £1,204 (scenario 3).

Table 36. Alzheimer disease model results

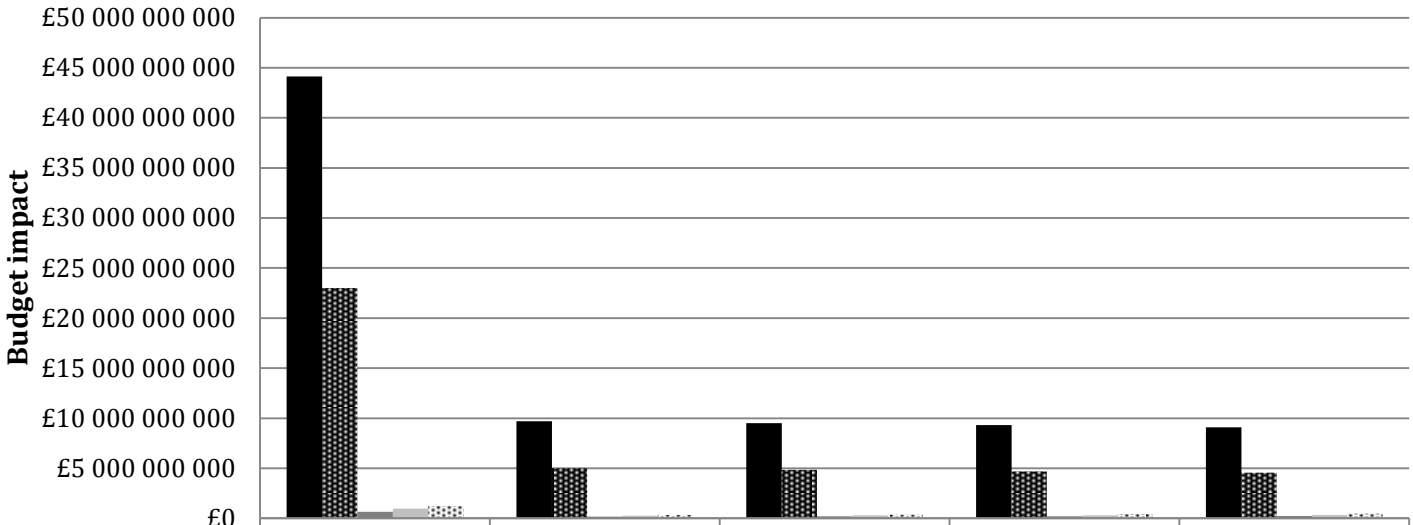
	Standard of care	ATMP Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Total cost (NHS) per patient	£10,290	£86,585	£50,219	£11,760	£12,442	£13,091
Total cost (Societal) per patient	£57,279	£86,585	£73,755	£59,547	£60,470	£61,606
QALYs	1.83	4.37	3.15	1.87	2.04	1.92
ICER (NHS)		£30,000/ QALY	£30,000/ QALY	£30,000/ QALY	£30,000/ QALY	£30,000/ QALY
ICER (societal)		£11,523/ QALY	£12,379/ QALY	£46,266/ QALY	£44,479/ QALY	£46,348/ QALY
ATMP price per patient		£86,585	£45,059	£1,204	£1,805	£2,291

3.2.2. Budget impact in Alzheimer disease

The 5-year total budget impact of an ATMP in AD varied between £81.7bn in scenario 1 and £1.4bn in scenario 3 (Figure 29). The highest budget impact is in the first scenario when the ATMP cured all patients, it was £44bn the first year and decrease to £9bn in the following years. The ATMP that cured 50% of patients had a budget impact of £23bn in the first year and around £5bn in the following years. ATMP that slowed down the disease progression had the lowest budget impact: £0.6bn in the first year followed by £0.2bn each year in scenario 3 and £0.9bn followed by almost £0.3bn each year in scenario 4.

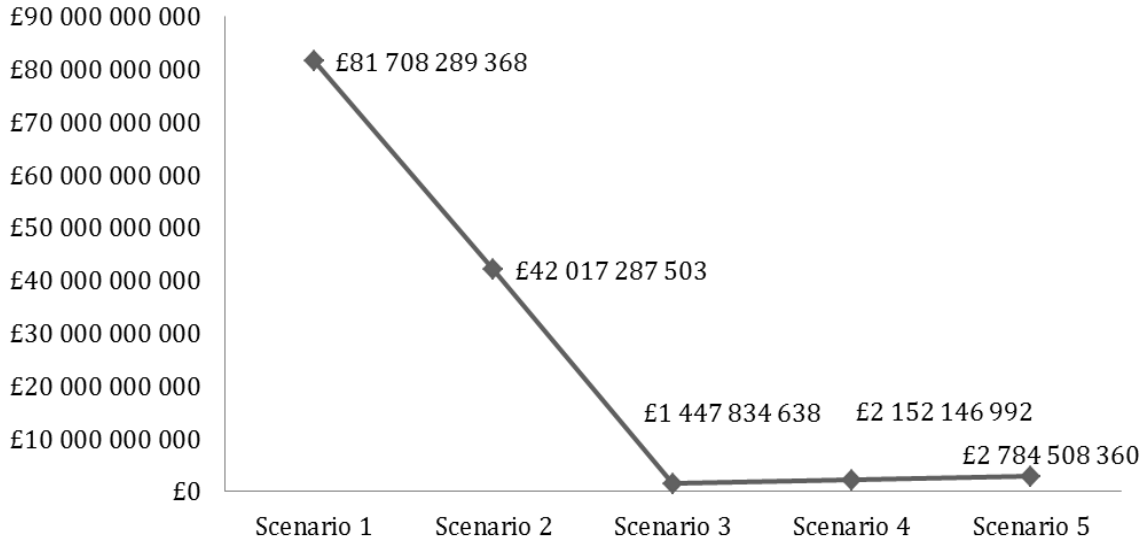
Scenario 5 where the ATMP stopped the disease progression, the total budget impact in the first year was £1.2bn and then £0.4bn each year (Figure 28).

Figure 28. Annual budget impact of ATMP in Alzheimer disease



	2016	2017	2018	2019	2020
Scenario 1	£44 122 078 889	£9 684 373 021	£9 505 005 844	£9 301 317 859	£9 095 513 756
Scenario 2	£22 992 127 605	£4 981 829 430	£4 822 383 824	£4 679 086 046	£4 541 860 598
Scenario 3	£639 185 943	£177 524 532	£186 451 505	£212 308 889	£232 363 770
Scenario 4	£957 524 139	£262 190 930	£285 933 829	£310 314 268	£336 183 826
Scenario 5	£1 216 672 815	£338 560 378	£373 480 263	£409 089 124	£446 705 781

Figure 29 : 5-year total budget impact per scenario

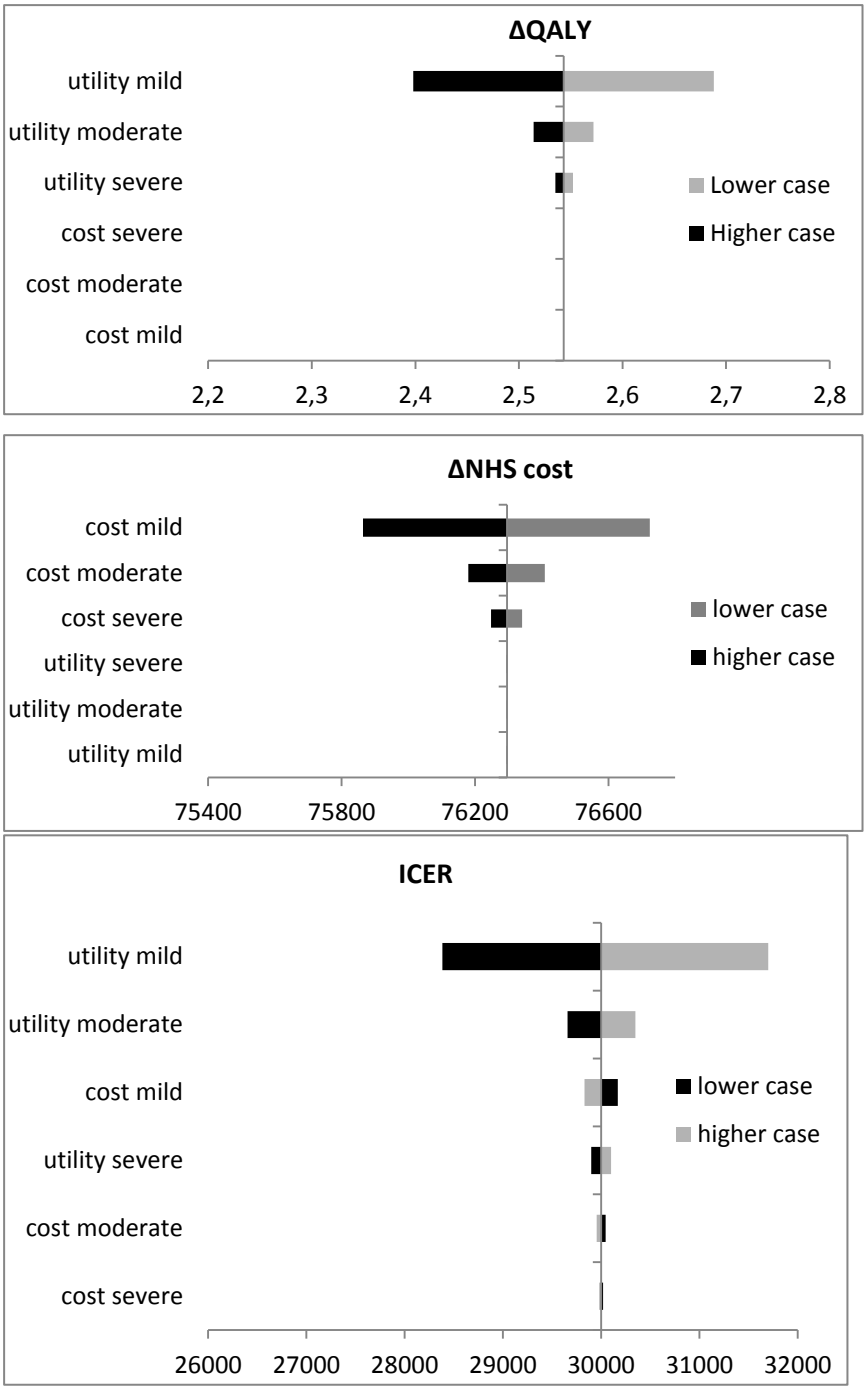


3.2.3. Sensitivity analysis

The sensitivity analysis showed that the model is highly sensitive to the utility of the mild stage. A 10% increase in the utility of the mild stage led to an ICER increase from £30,000/QALY to £31,700/QALY (3.3% increase). Figure **30** shows the tornado

diagrams for the difference in QALY, difference in NHS costs and the ICER.

Figure 30. Tornado diagrams



3.3. Heart failure results

3.3.1. Cost-effectiveness results and ATMP price

The costs and QALYs gained with SoC and ATMP in HF were shown in **Table 37**. In HF, the average discounted QALY gained for the standard of care alone was 3.72 and 7.49, 5.65, 3.85, 3.94, 4.10 for the ATMP in scenarios 1 to 5 respectively. The price of an ATMP

administration per patient varied between 198,882€ (scenario 1) and 7,028€ (scenario 3).

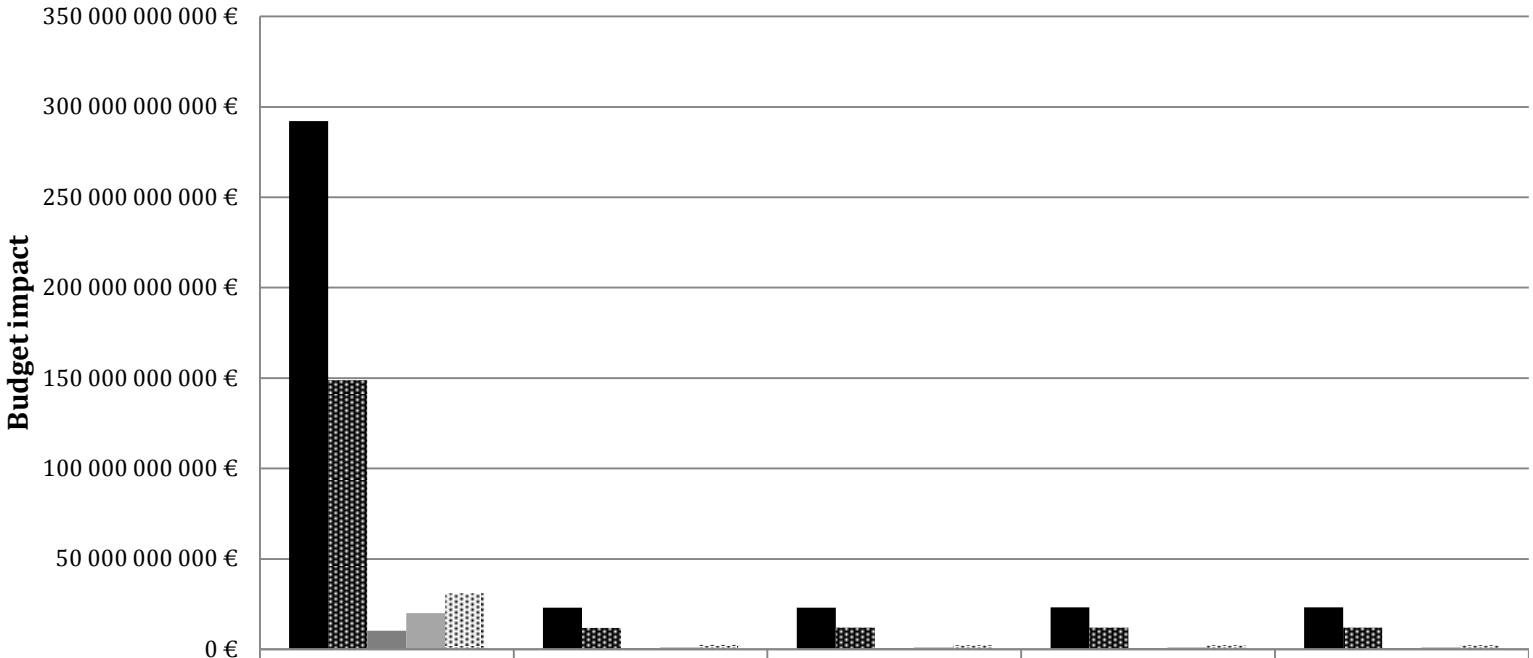
Table 37. Heart failure model results

	Standard of care	ATMP Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
Total cost per patient	10,413€	198,881€	106,479€	16,501€	21,275€	29,034€
QALYs	3.72	7.49	5.65	3.85	3.94	4.10
ICER	50,000 € /QALY	50,000 € /QALY	50,000 € /QALY	50,000 € /QALY	50,000 € /QALY	50,000 € /QALY
ATMP price per patient	-	198,682€	101,272€	7,028€	13,895€	20,843€

3.3.2. Budget impact in heart failure

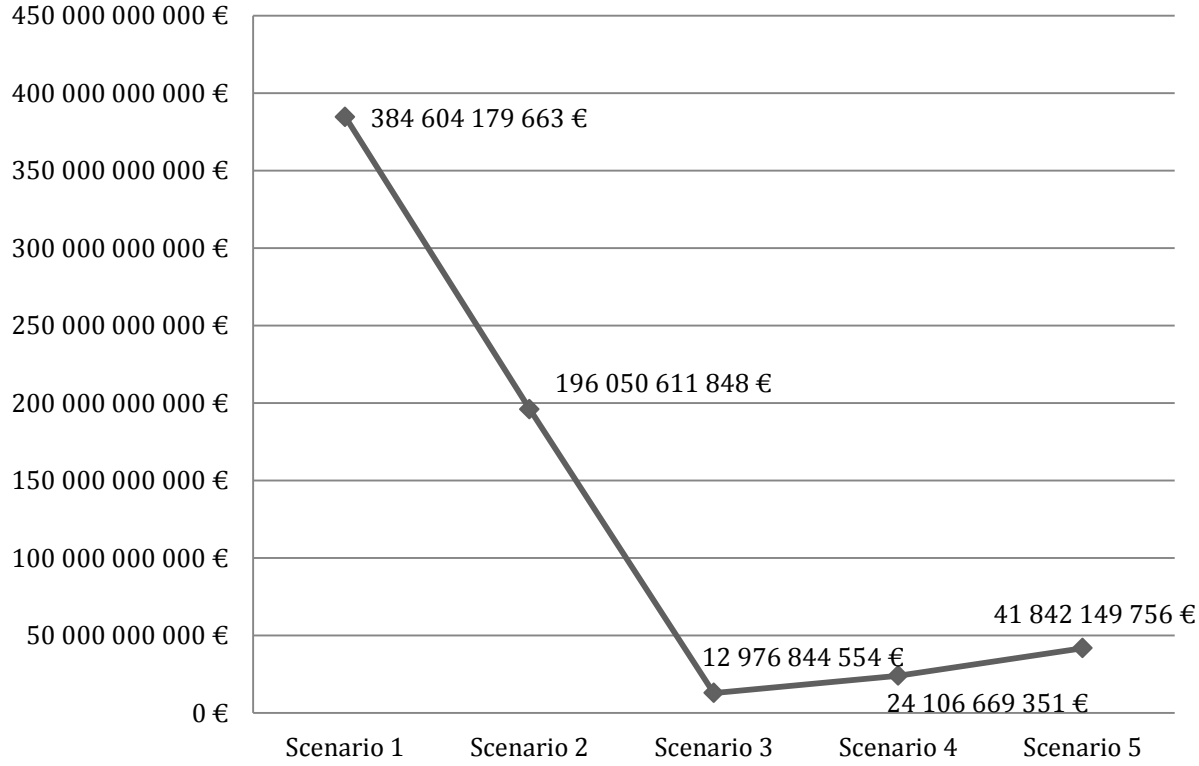
Budget impact analysis results are presented in Figure 31 and Figure 32. The 5-year net budget impact of an ATMP in HF varied between €384bn in scenario 1 and €13bn in scenario 3 (Figure 32). The highest budget impact is in the first scenario when the ATMP cured all patients, it was €292bn the first year and decrease to €23bn in the following years. The ATMP that cured 50% of patients had a budget impact of €148bn in the first year and €11bn in the following years. ATMP that slowed down the disease progression had the lowest budget impact: €10bn the first year followed by almost €0.7bn each year in scenario 3 and €20bn in the first year followed by €1bn each year in scenario 4. Scenario 5 where the ATMP stopped the disease progression, the net budget impact in the first year was €30bn and then €2bn each year (Figure 31).

Figure 31. Total budget impact per year of ATMP in heart failure



	2016	2017	2018	2019	2020
Scenario 1	292 089 944 795 €	22 967 922 673 €	23 083 448 106 €	23 196 368 514 €	23 266 495 574 €
Scenario 2	148 763 608 417 €	11 722 021 887 €	11 808 746 460 €	11 861 734 778 €	11 894 500 305 €
Scenario 3	10 288 487 575 €	714 241 512 €	671 004 007 €	653 666 762 €	649 444 699 €
Scenario 4	20 008 044 387 €	1 055 006 375 €	1 021 885 143 €	1 010 855 664 €	1 010 877 783 €
Scenario 5	30 746 461 969 €	2 277 415 502 €	2 152 030 381 €	2 089 198 074 €	2 063 890 660 €

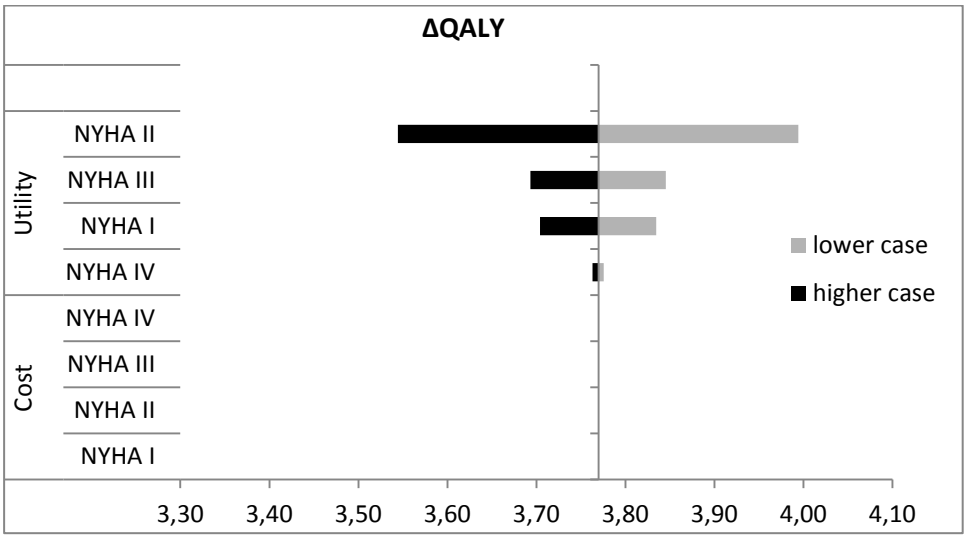
Figure 32. 5-year budget impact in heart failure per scenario

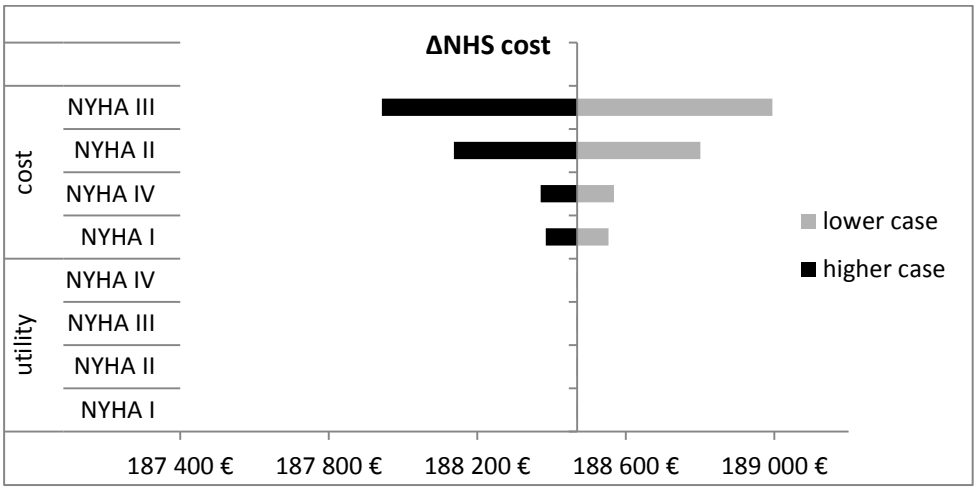


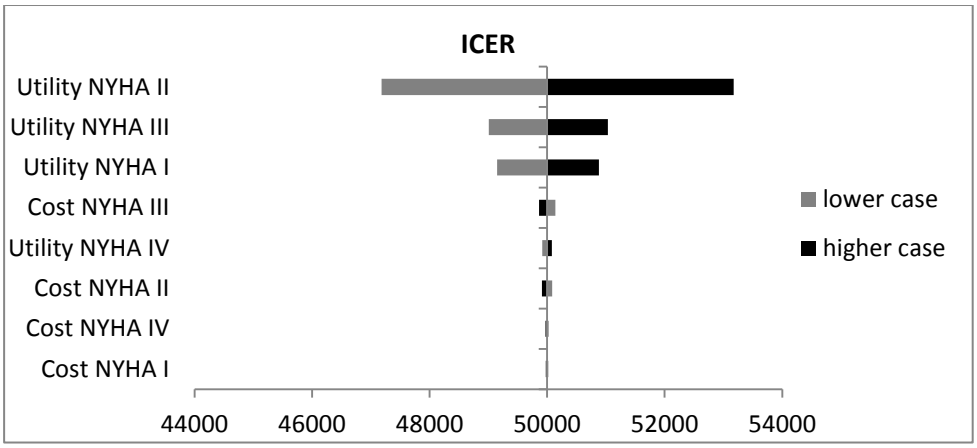
3.3.3. Sensitivity analysis

The sensitivity analysis showed that the model is highly sensitive to the utility of the NYHA II HF stage. A 10% increase in the utility of the NYHA II stage led to an ICER increase from €50,000/QALY to €53,174/QALY (6.3% increase). Figure 33 shows the tornado diagrams of the sensitivity analysis.

Figure 33. Tornado diagrams







4. Discussion

Chronic diseases impose a huge clinical and economic burden. As we have shown in Chapter 2, several novel therapies targeting chronic diseases are in development. The aim of this study was to evaluate the impact on health insurance budget of ATMPs if they will succeed to prove the expected clinical outcomes and fulfill the clinical unmet needs in many chronic diseases. AD, HF and PD were the examples that we used. The analysis was carried out with multiple efficacy scenarios in order to evaluate various assumptions. The considerations behind the choice of the diseases were the high medical unmet needs in these disease areas and the absence of curative therapies.

AD, PD and HF are chronic diseases that have no curative treatments nowadays. The latter imposes a huge global economic burden, estimated at $108 bn per annum by Cook C et al. 2014 (229). AD and PD have also a huge economic burden and the overall mean cost burden of both diseases – PD and AD- is expected to reach €357bn for the year 2050 in Europe if no new strategies were developed as demonstrated by Maresova P et al, 2016 study (230). This reflects the importance of novel curative therapies.

Several ATMPs in development may cure or halt the diseases. However, these therapies are expected to be rewarded by high premium prices, therefore increase the pressure on NHS that is already operating under budget constraints. No studies assessed the budget impact of introducing new ATMPs to the market.

The 3 diseases progressions were modeled in 3 Markov models. By fixing the ICER threshold at 30,000£/QALY for PD and AD and 50,000€/QALY for HF, we calculated the optimal price of a cost-effective ATMP. An increase in QALYs gained was observed in the 5 scenarios of the 3 conditions, especially in the first scenario where all patients were cured. On the other hand, the impact on NHS budget was expected to be very important.

A cost effective ATMP that cures all patients with AD, PD and HF would be priced as high as 86,585£, 190,312£ and 198,882€ per patient respectively. The ATMP price varied with the efficacy, the lowest price in the 3 cases was for the third scenario where ATMP slowed the disease progression by one third, it was 1,204£, 21,501£, and 7,028€ for AD, PD and HF respectively. The ATMPs prices identified in our study were reasonable and in the range of the prices usually claimed by manufacturers for novel drugs like cancer drugs for example and some ATMP prices like Chondrocelect® (20,000€), Provenge® (93,000$) and Imlygic® (65,000$). However, ATMPs prices may reach higher amounts depending on the disease mortality, target population, and utility. Indeed, Glybera® was

priced at €1.1million, and Strimvelis® was priced at 594,000€. And a new gene therapy has been approved by the FDA, with a claimed price of 475,000$ per patient (231). Furthermore, the curative CAR-T cell price was estimated £528,600 per patient via a value based approach in the NICE appraisal exemplar for a hypothetical CAR-T cell (71).

Given the huge volume of the target population, the budget impact of the cost-effective products was predicted to be very important. The five-year total budget impact in AD varied between £81bn and £1.4bn depending on the efficacy of the ATMP. The five-year net budget impact is expected to be between £29bn and £4bn if the ATMP respectively cures all patients with PD or slow down the disease progression by 50% without cu ring effect. In the case of HF where the target population is larger, the 5-year budget impact was higher: €384bn for the first scenario and €13bn for the third scenario. The expected budget impact of ATMPs is by far higher than the UK threshold of £20million above which a price negotiation needs to be done. Therefore, it is likely that ATMP manufacturers will need to have commercial discussions with NHS England in order to ensure ATMPs access to the English market.

Our results highlight the fact that cost-effective does not mean affordable therapy. Several EU countries use the cost-effectiveness analysis to compare the cost and consequences of two or more alternatives with a common therapeutic objective. A new cost-effective treatment seldom displaces all other treatment options (232). Our results showed that a cost effective therapy on a per-patient level can be unaffordable for payers. Cost-effectiveness threshold can be an aid for decision making (233) but may not be the key consideration for adopting advanced therapies. The budget impact is increasingly being used by heath care decision makers.

4.1. Analysis of impact of the shift from traditional therapies to ATMPs on the cost of diseases and health expenditure

Cost of the disease:

According to the dementia report published by the Alzheimer's Society, the annual cost of Alzheimer in UK reached £26bn of which £4.3bn picked up by the NHS (177). The cost of Parkinson in UK was estimated by Findley et al. (234) between £449M and £3.3bn annually. In addition, McCrone et al. (235) estimated the total PD cost per patient to £13,804. Considering the PD prevalence previously used of 119,351 patients, the total

cost is around £1.65bn. The annual total cost of HF in France was £2.5bn (Tuppin et al. (236)) representing 10% of total health expenditure.

The use of ATMPs for PD patients is expected to increase the illness cost during the first year between 1452% and 264% depending on the efficacy scenario of the ATMP. Similarly, switching to ATMPs in AD will increase the cost of the disease between 137% and 101%. And the administration of ATMPs for all HF patients is expected to increase the cost of HF between 1016% and 128%. Furthermore, the cost of disease will continue to increase during the second and following years with a less important impact (Table 38). Therefore, ATMPs are expected to substantially increase the cost of the diseases especially in the first year if the cost is paid upfront by payers.

Table 38. Impact of ATMPs on the cost of disease

	Cost of disease	Budget impact in the first year	Budget impact in the second year	Impact on the cost of disease in the first year	Impact on the cost of disease in the second year
PD					
Scenario 1	£1.65bn	£22.3bn	£1.6bn	+1452%	+197%
Scenario 2	£1.65bn	£12.1bn	£0.885bn	+833%	+154%
Scenario 3	£1.65bn	£2.7bn	£0.35bn	+264%	+121%
Scenario 4	£1.65bn	£3.9bn	£0.45bn	+336%	+127%
Scenario 5	£1.65bn	£7.7bn	£0.77bn	+567%	+147%
AD					
Scenario 1	£26bn	£44.1bn	£9.7bn	+270%	+137%
Scenario 2	£26bn	£22.9bn	£4.98bn	+188%	+119%
Scenario 3	£26bn	£0.64bn	£0.17bn	+102%	+101%
Scenario 4	£26bn	£0.957bn	£0.26bn	+104%	+101%
Scenario 5	£26bn	£1.2bn	£0.34bn	+105%	+101%
HF					
Scenario 1	€2.5bn	£292bn	£22.9bn	+11780%	+1016%
Scenario 2	€2.5bn	£148.7bn	£11.7bn	+6048%	+568%
Scenario 3	€2.5bn	£10bn	£0.71bn	+500%	+128%

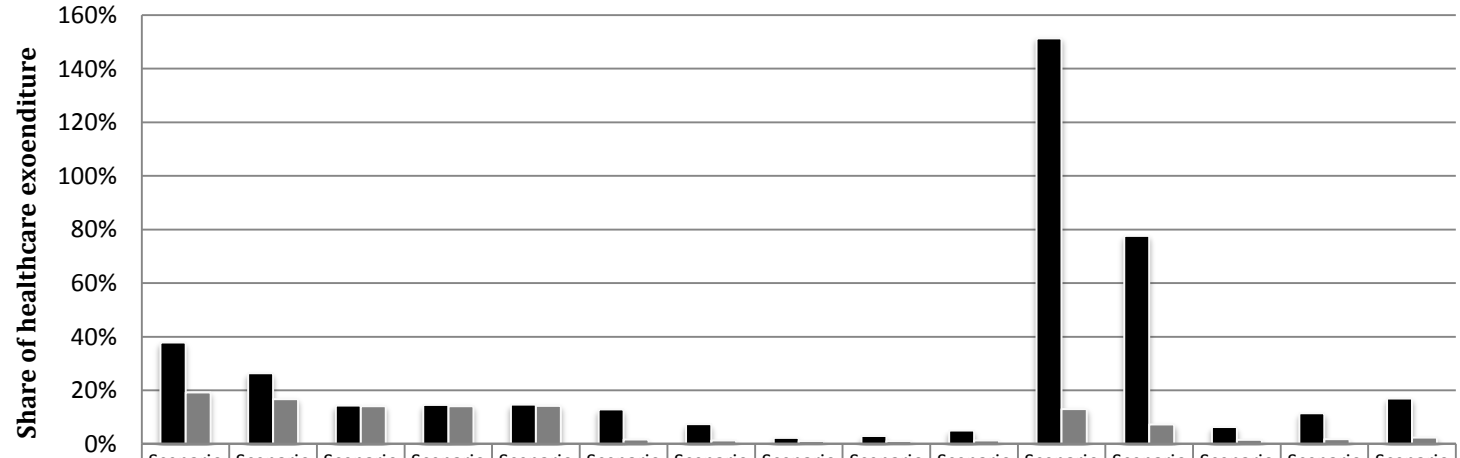
Scenario 4	€2.5bn	£20bn	£1.05bn	+900%	+142%
Scenario 5	€2.5bn	£30.7bn	£2.27bn	+1328%	+191%

Health expenditure:

Based on OECD data, the healthcare expenditure in UK in 2016 is estimated 9.7% of GDP, equivalent to almost £185bn and the healthcare expenditure in France in 2016 is estimated 11% of GDP equivalent to €194bn (237).

According to the results of the model, the share of the annual healthcare expenditure by ATMPs during the first year is predicted to be between 37% and 14% in the case of AD, between 13% and 2% in the case of PD. However in the case of HF, due to the large target population, a large budget is required to pay for an ATMP for all the HF patients, therefore the predicted impact of an ATMP that can cure all HF patients (Scenario 1) was exceeding the annual healthcare expenditure budget and reached 151% of the annual healthcare expenditure, and for the other scenarios it varied between 78% and 6%. The share of health spending will decrease significantly in the second year (Figure 34).

Figure 34. Predicted share of annual healthcare expenditure by ATMPs



	AD					PD					HF				
	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5	Scenario 1	Scenario 2	Scenario 3	Scenario 4	Scenario 5
First year	38%	26%	14%	15%	15%	13%	7%	2%	3%	5%	151%	78%	6%	12%	17%
Second year	19%	17%	14%	14%	14%	2%	1%	1%	1%	1%	13%	7%	2%	2%	2%

Our results showed possible scenarios for future health spending growth ranging from 2% of healthcare spending to rates well above the annual health expenditure. Chronic diseases are on the rise, the innovation will increase the global cost and the burden on healthcare systems. If healthcare systems can ensure the budget required for one

disease, would it be possible to ensure the budget to pay for ATMPs in all chronic diseases?

4.2. Total cost of ATMPs in chronic diseases and orphan diseases

In order to take our analysis further, we suggested that ATMPs targeting 35 different diseases will successfully reach the market, the diseases were: 15 chronic diseases with important clinical unmet needs and the 20 most prevalent orphan diseases. The cost of an ATMP administration for a chronic disease was considered 100,000€ and an ATMP for orphan diseases price was considered 3 to 4 times higher than an ATMP for chronic disease, we suggested a price of 350,000€. The objective of this analysis was to estimate the total cost of ATMPs.

Table 39 shows the predicted cost per disease and the total cost for chronic diseases and orphan diseases for the first year and the second year.

Table 39. ATMPs predicted costs for orphan and chronic diseases

Diseases	Prevalence	Incidence	Cost of ATMPs the first year	Cost of ATMPs the following year	Reference
Chronic Diseases					
Osteoarthritis	9 000 000	64 837	€900bn	€6.5bn	(238)
Peripheral Arterial Obstructive Disease	6 483 792	194 513	€648bn	€19bn	(239)
Chronic Obstructive Pulmonary Disease	3 500 000	181 546	€350bn	€18bn	(240, 241)
Asthma	3 500 000	5 000	€350bn	€0.5bn	(242, 243)
Diabetes	3 300 000	146 000	€330bn	€14.6bn	(244, 245)
Chronic kidney disease	3 000 000	71 322	€300bn	€7bn	(246, 247)
Ischemic heart disease	1 810 000	291 771	€181bn	€29bn	(248)
Heart failure	1 491 272	130 000	€149bn	€13bn	(227, 228)
Cerebrovascular diseases	770 000	140 000	€77bn	€14bn	(249, 250)
Alzheimer & dementia	770 000	225 000	€77bn	€22.5bn	(251, 252)
Cirrhosis	700 000	12 967	€70bn	€1.3bn	(253, 254)

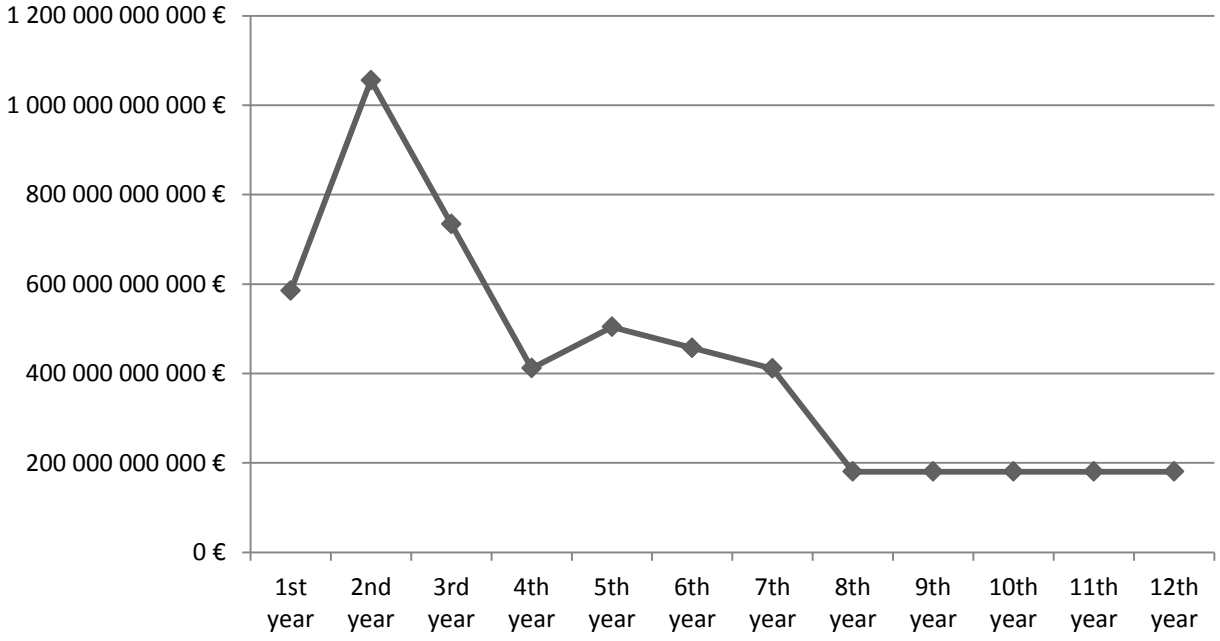
Breast cancer	220 000	174 000	€22bn	€17.4bn	(255)
Rhumatoid polyarthritis	180 000	5 706	€18bn	€0.57bn	(256)
Parkinson	160 000	19 451	€16bn	€1.9bn	(257)
Crohn disease	72 500	3 825	€7.25bn	€0.38bn	(258)
Orphan diseases					
Brugada syndrome	32 419	9 207	€11bn	€3bn	(259, 260)
Protoporphyria, erythropoietic	32 419	713	€11bn	€0.25bn	(259, 261)
Melanoma, familial	30 344	720	€10.7bn	€0.25bn	(259, 262)
Scleroderma	27 232	65	€9.5bn	€0.02bn	(259, 263)
Non-Hodgkin malignant lymphoma	19 451	6 282	€6.8bn	€2bn	(259, 264)
Myeloma, multiple	16 858	3 287	€5.9bn	€1.1bn	(259, 265)
Coffin-Lowry syndrome	14 589	1 297	€5bn	€0.45bn	(259, 266)
Polycythemia vera	16 209	648	€5.6bn	€0.22bn	(259, 267)
Rendu-Osler-Weber disease	13 778	68	€4.8bn	€0.22bn	(259, 268)
Microdeletion 22q11	12 968	3 242	€4.5bn	€1.1bn	(259, 269)
Ehlers-Danlos syndrome, classic	12 968	196	€4.5bn	€0.68bn	(259, 270)
Stickler syndrome	8 753	105	€3bn	€0.036bn	(259, 271)
Glioblastoma	7 132	2 670	€2.5bn	€0.9bn	(259, 272)
Cystic fibrosis	6 484	224	€2.2bn	€0.078bn	(259, 273)
Hodgkin disease	6 095	874	€2bn	€0.3bn	(259, 274)
Rett Syndrome	5 317	2 788	€1.8bn	€0.97bn	(259, 275)
X-linked severe combined immunodeficiency, T- B+	973	4	€0.34bn	€0.010bn	(259, 276)
Gaucher disease	648	1081	€0.2bn	€0.3bn	(181, 259)
Mucopolysaccharidosis type 1	648	8	€0.2bn	€0.02bn	(259, 277)

Neuroendocrine tumor	648	4 539	€0.2bn	€1bn	(259, 278)
Total			€3.6tn	€180bn	

Bn: billion (10^9)
Tn: Trillion (10^{12})

A second hypothesis was analyzed: we considered that 5 ATMPs, randomly selected, will reach the market every year. The results of this analysis are shown in Figure 35.

Figure 35. ATMPs budget



If an ATMP will reach the market for 35 different diseases, a budget of €3.6trillion is needed to pay for the treatment of the patients in the first year. This number will decrease to €180bn in the second year thanks to the expected suggested efficacy of the ATMP that will cure the patients. In the second scenario, where we considered that 5 ATMPs will reach the market every year, the budget will fluctuate between €1tn and €500bn per year for the first 7 years, then the budget tend to stabilize around €180bn. However, the annual pharmaceutical spending in France is around €40bn (5) which is by far less than the budget required to pay for ATMPs. Therefore, our analysis shows that is unlikely that payers can afford ATMPs and pay the whole cost upfront.

5. Limitations

As with any model, our study does have its limitations. The most important limitation is related to data availability. Up-to-date cost data were limited; however the costs were

actualized using the CPI and the sensitivity analysis showed the minor effect of the costs on the model results. In addition, the current analyses conducted only a number of scenarios in terms of treatment decisions varying between best case scenario and worst case scenario, additional analyses evaluating the ATMPs with real world effectiveness data would be valuable.

Some controversies exist among health economists about whether health care costs (not specifically related to life-years gained) over additional life-years costs should be included. In our study, those costs were not included. NICE guidelines are unclear about this, in the NICE health technology appraisal 2013 it was mentioned: "*Costs that are considered to be unrelated to the condition or technology of interest should be excluded*" (279). In reality, those costs are rarely included in the analyses.

The deterministic sensitivity analyses were also subject to limitations; the variance figures around estimates were unavailable in some cases, and a standard error of 10% of the mean was assumed. Finally, in the chronic diseases cost evaluation, European prevalence and incidence data were considered when French data were not available.

6. Conclusion

Innovation always comes with a cost but can payers afford this cost?

As we have shown, the cost of ATMPs is expected to reach unaffordable levels. The case of ATMPs that we have highlighted reminds of the Sovaldi® case previously described. While being cost-effective, Sovaldi® high price compromised patient access to this effective therapy and has put an unsustainable strain on healthcare budgets.

ATMPs are expected to threaten the sustainability of healthcare system if an important number of ATMPs will successfully reach the market and prove an important efficacy to treat diseases with clinical unmet needs. While governments are trying to reduce health spending by applying cost-containment procedures, the expected fast pace of ATMPs can increase the pressure on governments and payers. The pressure will be at social level and economic level:

- Payers will need to ensure the sustainability of the healthcare system, to try to reduce the spending by cutting the pharmaceuticals costs,

- At the same time, there is a need to reward innovation in order to incentivize the pharmaceutical companies to invest in the R&D of innovative breakthrough treatments that can cure diseases with high unmet needs.
- And patients suffering from untreatable chronic diseases will increase the pressure on payers by requesting access to innovation that can cure their diseases.

Payers will need to find a solution to balance the 3 aspects.

Prioritizing a disease may be a solution that can be convenient by ensuring a budget for ATMP in one disease. However, prioritizing cancer disease for example and ensuring treatment for cancer disease while limiting the patient access for AD therapies would be ethically unacceptable. Equity of care was always a concern for payers (280).

As a summary, the innovation may outpace the affordability using the traditional payment models especially in the short term. In the next chapter, we will discuss the proposed health policies reforms to pay for innovative therapies and we will suggest a solution to mitigate the ATMP funding challenge.

Chapter 4: Funding of ATMPs

1. Introduction

The sustainable funding of innovative expensive therapies constitutes a major challenge currently facing the payers worldwide. As we have shown in chapter 2, a growing number of ATMPs is in the pipeline. Those breakthrough therapies aim to treat several conditions and diseases that were previously considered incurable. Innovation is associated with a high price; provision of these therapies tend to be one of the most resource-consuming tasks (281). "Skyrocketing" prices are a source of public furor. Those expensive therapies are arriving to the market while governments are trying to cut and reduce the pharmaceutical expenditures. Indeed, the price of Glybera® has reached €1.1 million per patient, Strimvelis® 594,000€ per patient. In August 2017, the FDA approved the first CAR-T cell therapy in US, Kymriah® (tisagenlecleucel) which is priced by Novartis, its manufacturer, at 475,000$ per treatment. The latter is also expected to reach the European market soon.

The need for new payment models was an issue raised in several journal papers, blogs, etc… especially after the approval of Kymriah® in the US (282, 283).

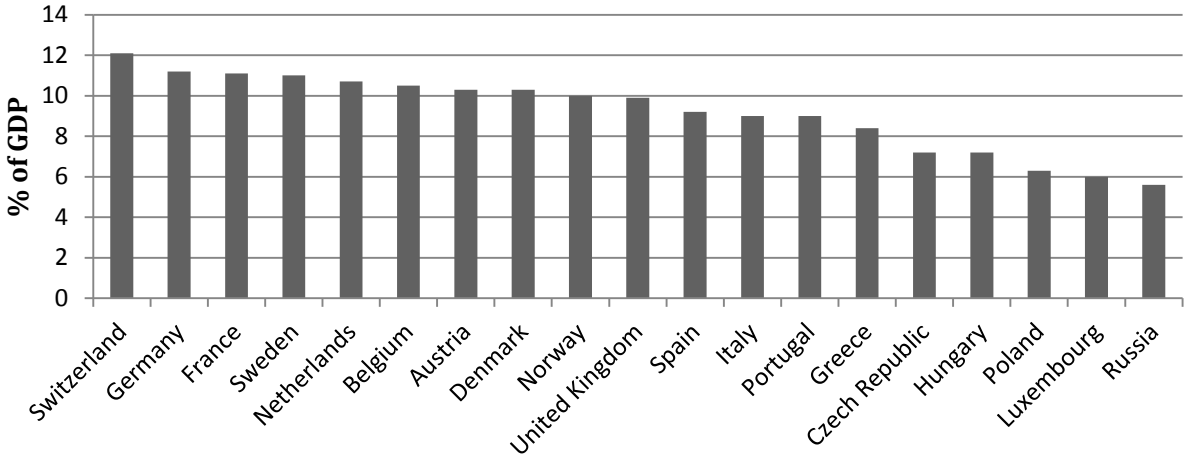
In addition, the French Ministry of Health launched a new initiative to promote an international dialogue between stakeholders on access to innovative therapies and sustainability of pharmaceutical spending. The OECD is managing this initiative called "*Sustainable access to innovative therapies*" and an online consultation was having place between March 13 and May 2017 (284).

We will start with a short review of the current economic situation and current pricing policies then we will present our study and discuss the new funding models for innovation.

1.1. Current economic situation

Healthcare expenditure tends to increase; around 10% of the GDP is spent on health care in EU (237). Figure 36 shows the percentage of GDP spent on healthcare in several European countries. Health spending includes personal health care (curative care, rehabilitative care, long-term care, ancillary services and medical goods) and collective services (prevention and public health services as well as health administration), but excluding spending on investments.

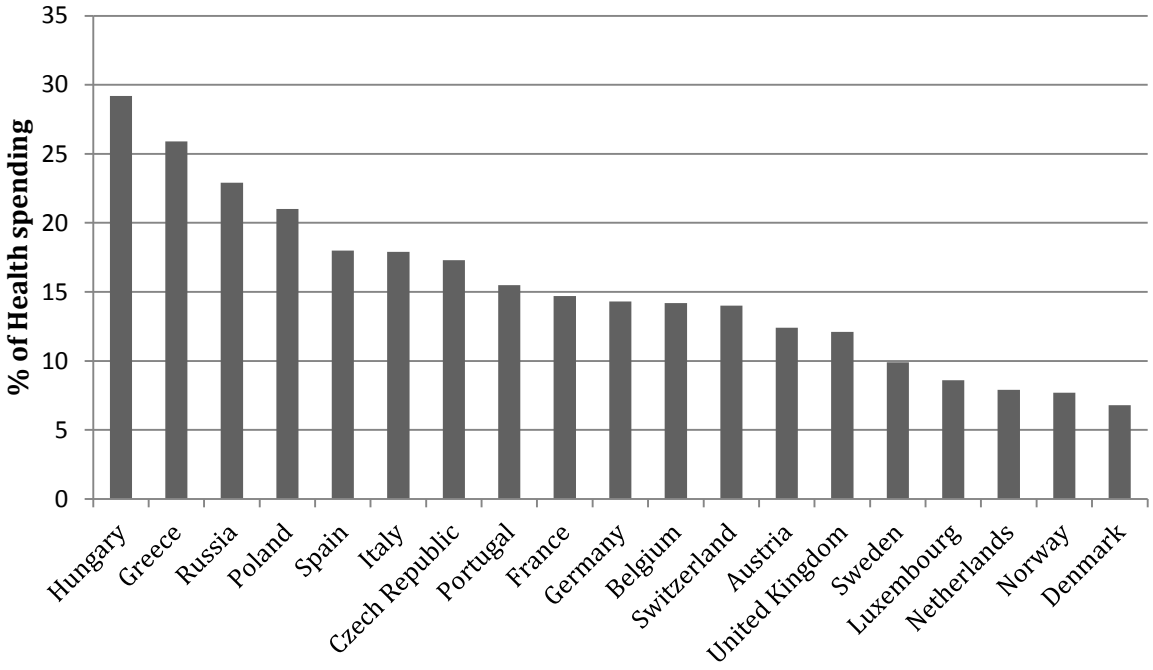
Figure 36 : Health expenditure as part of GDP, 2015



This graph was created based on data from OECD website (237). This graph shows the percentage of GDP spent on healthcare in 19 European countries.

Based on OECD data (5), pharmaceuticals expenditure constitutes an important part of healthcare expenditure (Figure 37). Pharmaceutical spending covers expenditure on prescription medicines and over-the-counter products or self-medication excluding the pharmaceuticals consumed in hospitals and other health care settings. Final expenditure on pharmaceuticals includes wholesale and retail margins and value-added tax and total pharmaceutical spending refers in most countries to "net" spending, i.e. adjusted for possible rebates payable by manufacturers, wholesalers or pharmacies (5).

Figure 37 : Pharmaceuticals expenditure, 2015

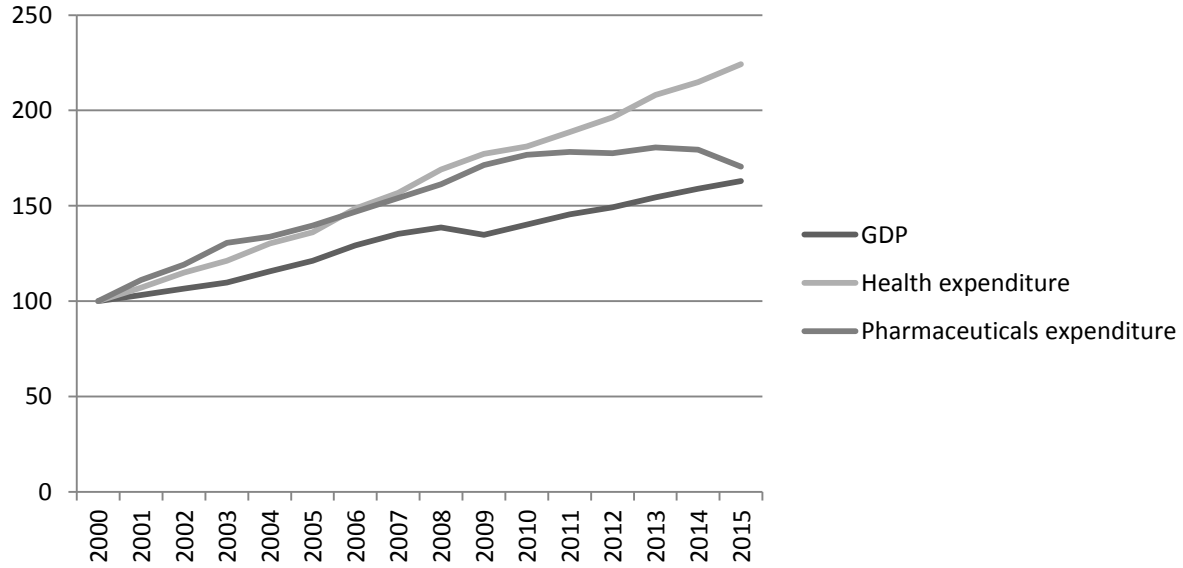


This graph was created based on data from OECD website (5). It shows pharmaceuticals expenditure of the total health spending in 19 European countries.

The variation in pharmaceutical expenditures across countries raises questions about which countries may be over- or under-spending, benchmarks for such assessments are undefined.

After comparing the GDP, pharmaceutical expenditures and health expenditures excluding pharmaceuticals, based on OECD data, it was shown that both pharmaceutical and total health expenditures grew at a higher rate than the mean annual growth rate of GDP for the OECD countries between 2000 and 2015. Pharmaceuticals growth was higher than health expenditure between 2000 and 2006, and then the health expenditure growth surpassed that of pharmaceuticals (Figure 38).

Figure 38. Trend growth in pharmaceutical expenditure, health expenditure and GDP between 2000 and 2015



Source: OECD data
GDP: Gross Domestic Product
Notes: values are average value for total OECD countries: Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Israel, Italy, Japan, Korea, Latvia, Luxembourg, Mexico, Netherlands, New Zealand, Norway, Poland, Portugal, Slovak Republic, Slovenia, Spain, Sweden, Switzerland, Turkey, United Kingdom, United States.
Pharmaceutical expenditure is excluded from health expenditure. 2000 values were considered as 100.

1.2. Current pricing and reimbursement policies

Under the continued austerity, payers are trying to limit pharmaceutical spending by applying cost-cutting initiatives. They are scrutinizing the additional value of new products and are seeking a greater value for money. Policy makers attempt to control pharmaceutical expenditures using a range of tools, including control of prices and/or volumes (e.g. price-volume agreements). Some policies control the level of spending for

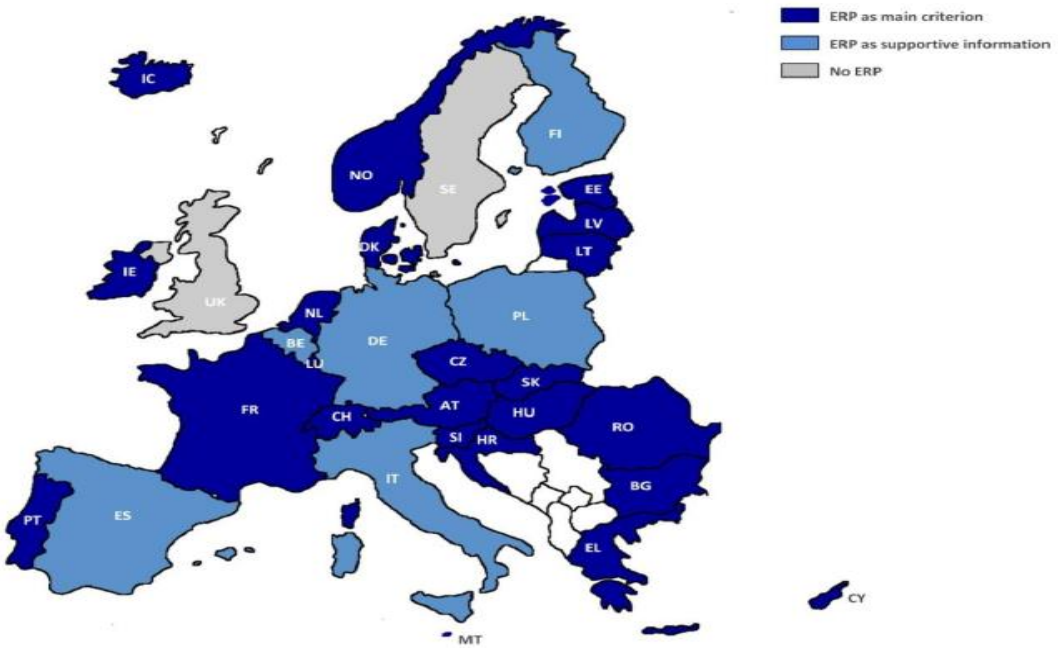
particular products (e.g., product-specific rebates) or for pharmaceuticals generally (e.g., claw-backs, patient cost-sharing).

In a recently published WHO report on access to new medicines in Europe (160), the policies for the introduction of new high-cost medicines were reviewed and evaluated. Among the pricing policies cited in this report were: free pricing, rate of return regulation, external reference pricing, cost plus pricing, clinical and cost-effectiveness pricing, value based pricing and price revision (mandatory price cuts). In addition to pricing policies, the reimbursement in Europe is based on Health Technology Assessment (HTA) through the use of economic and clinical evidences and budget impact assessments. Countries use more than one method for the pricing and reimbursement processes.

1.2.1. External reference pricing

The WHO Collaborating Centre for Pricing and Reimbursement Policies defines external price referencing as: "The practice of using the price(s) of a medicine in one or several countries in order to derive a benchmark or reference price for the purposes of setting or negotiating the price of the product in a given country"(285). External reference pricing (ERP) also called "International reference pricing" has become one of the most common cost-containment tools to reduce prices for in-patent pharmaceuticals in the EU Member State (Figure 39)(286). External benchmarking of pharmaceutical prices in other jurisdictions is the most widely used technique to limit prices or reimbursement prices in OECD countries except Germany and UK (287). Germany and UK are often first-launch countries, they allow free pricing for innovative drugs, they constitute together with France the three countries most commonly referenced. ERP is not conceptually considered as appropriate method to contain pharmaceuticals expenditure but it could be an effective tool (286).

Figure 39. Overview of ERP across Europe



ERP: External Reference Pricing, AT, Austria; BE, Belgium; BG, Bulgaria; CH, Switzerland; CY, Cyprus; CZ, Czech Republic; DE, Germany; DK, Denmark; EE, Estonia; EL, Greece; ES, Spain; FI, Finland; FR, France; HR, Croatia; HU, Hungary; IE, Ireland; IS, Iceland; IT, Italy; LT, Lithuania; LU, Luxembourg; LV, Latvia; MT, Malta; NL, the Netherlands; NO, Norway; PL, Poland; PT, Portugal; RO, Romania; SE, Sweden; SI, Slovenia; SK, Slovakia; UK, United Kingdom
This graph was published in Remuzat C et al, 2015 (286)

1.2.2. Internal reference pricing

This approach is mainly used to define the price or reimbursement price of generic drugs and, less commonly, therapeutic alternatives, at market entry. It consists of pricing drugs by reference to therapeutic comparators.

For example, France considers the degree of innovativeness of a new therapy for the purpose of price negotiation of new drugs being considered for addition to the positive list. the Transparency Commission (Commission de transparence) assesses the therapeutic value of each new drug being considered for reimbursement, as well as its incremental actual benefit over existing alternatives (Amélioration du service medical rendu), and rates the degree of innovation according to a five-level scale. Category V (with no improvement) will be required to offer a lower price than existing comparators to access the positive list.

1.2.3. Value-based pricing

Value-based pricing (VBP) terminology means a price that reflects the value to the customer (288). In healthcare sector, VBP is a pricing model where the price is linked to

evidence-based assessments of value for patients and the society of a new therapy. It "*sets prices based on a value assessment that takes into consideration a wider range of criteria than clinical cost–effectiveness, including the burden and severity of the disease and long-term benefits of the treatment*" (160).

Value assessment takes into account the pharmaceuticals clinical benefit and/or cost–effectiveness compared to alternative treatments. VBP frameworks started to be used after the shift towards relying on HTAs. Theoretically, a reimbursement amount per incremental QALY would be set by payers. Dimensions to be included to measure the value need to be clearly identified.

In France, French health authority (HAS), consider the level of innovation in five "Improvement in actual benefit" levels (IAB or ASMR) which help to determine drug prices. Under the 2012 Law for the Financing of Social Security, HAS was mandated to consider cost–effectiveness in its drug evaluations from October 2013 for drugs with:

1) major, important, or moderate IAB (IAB I, II, or III) claimed by the company and

2) drug with significant impact on the health insurance budget (threshold set at €20 million annual revenue after the second year of commercialisation), through its impact on care organisation, professional practices, or patient care and – when applicable – the drug's price (164).

In Germany, the Institute of Quality and Efficiency in Health Care (IQWIG) assesses the drug's additional therapeutic benefit. The assessment results are used in price negotiations between the Federal Association of Statutory Health Insurance Funds and the company based on the drug's perceived level of additional benefit. Drugs that fail to demonstrate additional benefit are assigned to a reference price group (289).

In Italy, the Italian Medicines Agency uses the innovation assessment algorithm to assess the level of innovation of new drugs and for price negotiations. The therapeutic innovation score is composed of the seriousness of the disease, availability of alternative treatments and therapeutic effect; it is classified as "important", "moderate" or "modest". Pharmaceuticals are divided into three categories: drugs for fatal or serious conditions that result in permanent disability or hospitalization, that reduce the risk of serious diseases and for non-serious conditions (290).

Novel therapies are increasingly reaching the market with limited evidence which lead to uncertainties that complicates decision-making. Payers started concluding risk-sharing agreements when evidence of cost-effectiveness is low. Under a risk-sharing agreement, a pharmaceutical company and coverage decision-makers agree on the expected outcomes from a drug in a given indication. If the drug fails to fulfil these expectations, the pharmaceutical companies refund the health service for the costs.

VBP for pharmaceuticals is part of health technology assessment, quality of care measurement and pay-for-performance payments for health professionals and institutions. All these policies aim to change resource allocation decisions on the basis of the respective values of health care interventions (291).

1.2.4. Other pricing methods

Other techniques to limit the prices or set the reimbursement prices of pharmaceuticals are less commonly used (287, 292):

1.2.5. Cost based pricing

Cost-based or Cost-plus pricing is : "*a method for setting retail prices of medicines by taking into account production cost of a medicine together with allowances for promotional expenses, manufacturer's profit margins, and charges and profit margins in the supply chain*" (293).

It is generally not recommended as an overall pharmaceutical pricing policy. It is used in some low- and middle-income countries e.g China, Vietnam, Bangladesh, Indonesia and in high-income countries including Australia, Greece and Spain, but it is usually confined to locally produced pharmaceuticals.

In addition, some orphan drugs are far from meeting the cost-effectiveness thresholds in VBP frameworks. Cost-based pricing may constitute a solution as it leads to a reasonable price (294).

1.2.6. Profit control as an indirect price control

The UK uses indirect price control by limiting pharmaceutical companies' profits on UK territory. Manufacturers are free to set the price at market entry. Further increases are limited by the Pharmaceutical Price Regulation Scheme (PPRS). If a company's rate of

profit exceeds the authorised level, it must reduce the general price level of its products in a way designed to pay back excessive returns to the NHS, but it remains free to decide on which products will see price reductions and to increase prices of other products.

1.2.7. Discounts, rebates, expenditure caps, and price-volume agreements

Discounts and rebates are price reductions and refunds linked to sales volume. A mix of various types of discounts and rebates is common. These mechanisms are gaining importance in Europe, discounts and rebates are being granted to public payers by pharmaceutical companies in 25 of the 31 European countries surveyed in a European survey (out-patient sector in 21 countries and in-patient sector in all 25 countries) (295).

An expenditure cap is a type of agreement between manufacturers and payers where the expenditures of the payers on a given drug are capped at a predefined amount. These agreements are usually put under risk-sharing agreements (296).

Pharmaceutical firms may negotiate based on the total value of sales, rather than on a per-unit price basis. Price reductions are obtained when volume increases through these agreements. The French pricing committee (Comité Economique des Produits de Santé: CEPS) sometimes enters into volume-price agreements for products with high sales potential, the “price reduction” takes the form of rebates, paid at the end of the year by the manufacturer with no consequences for the listed price.

1.2.8. Tendering

Tenders are mainly applied to generics market. Tenders are issued and the lowest price bidder wins the right to supply the market. Tenders ensure savings.

Procurement and tendering approaches are also used in many countries for purchasing hospital products.

1.3. Objective

While the pressure put on governments to fund more expensive therapies, new funding models are needed. Payers and policy makers need guidance to mitigate the challenges in creating a balance between encouraging and incentivizing the investment in research

and development of breakthrough therapies on one hand and on financing innovative medicines in a way that ensures the financial sustainability of the healthcare system.

Many studies have suggested new funding models for high-cost therapies in order to mitigate the affordability challenge.

The aims of this study were to identify, define, classify and compare the proposed approaches to funding innovative high-cost medicines proposed in the literature, to analyze their appropriateness for ATMPs funding and to suggest an optimal funding model for ATMPs.

2. Methods

The work in this chapter was divided in 6 steps:

1. Systematic literature review:

   A systematic literature review of funding models for innovation and high-cost drugs was conducted. A search strategy was developed and run in both Ovid Medline, and Embase in addition to grey literature search. Studies published between 2010 and February 2017 were selected. The following section presents an overview of the literature search methodology (literature sources, inclusion and exclusion criteria and data extraction).

2. Data extraction:

   After identifying the relevant articles, funding models for innovation and high-cost drugs definition, advantages and limitations were extracted from the included papers.

3. Classification:

   The identified funding models were classified in different categories and subcategories based on the nature of the agreements.

4. Comparison:

   In the fourth step, a comparison between the features of the identified funding models was conducted: the feasibility, acceptability, burden, financial interest, appeal for payers, and appeal for manufacturer.

5. Discussion:

   The appropriateness of each model to fund ATMPs was assessed and discussed

6. Recommendation

Based on all the information from the previous steps, an optimal sustainable funding model was recommended for ATMPs.

2.1. Literature review

2.1.1. Literature sources

The search was implemented in the following databases:

- Medline and Medline in process (access via the Ovid interface)
- EMBASE (access via the Ovid interface)

In addition, we conducted a search in the grey literature to identify existing references providing outputs of interest. To ensure capturing all relevant published papers, we cross referenced all articles from the bibliography of selected articles.

2.1.2. Search time Frame

Studies published between January 2010 and February 2017 were selected.

2.1.3. Language

Language is limited to English and French studies.

2.1.4. Search strategies for bibliographical databases

The following keywords were used: funding, financing mechanism, pay and innovation, cost control. A search strategy was developed for:

- Medline: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present (Table 40)
- Embase: 1974 to 14 February 2017 (Table 41)

Table 40. Medline and Medline in process search strategy

ID	Category	Search terms	Hits
#1	Funding models	exp Reimbursement, Incentive/ec [Economics]	664
#2		exp Risk Sharing, Financial/ec [Economics]	79
#3		"Costs and Cost Analysis"/ec [Economics]	505
#4		managed entry agreement$.mp.	20
#5		funding model$.ab,ti.	298

ID	Category	Search terms	Hits
#6		"financ* mechanism$".ab,ti.	425
#7		pay*.mp.	87,312
#8		#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7	89,303
#9	High cost drugs	(high cost*.ti,ab.) AND (drug$.mp. or Pharmaceutical Preparations/)	3016
#10		High drug$ pric*.mp.	34
#11		(innovat* and drug$).mp.	14,938
#12		gene therapy.mp. or Genetic Therapy/	63,564
#13		cell therapy.mp. or "Cell- and Tissue-Based Therapy"/	19,171
#14		#9 OR #10 OR #11 OR #12 OR #13	100,723
#15	**Final**	#8 AND #14	3,236

Table 41. Embase search strategy

ID	Category	Search terms	Hits
#1	Funding models	*reimbursement/ and drug$.ab,ti.	1,084
#2		exp "cost control"/	58,904
#3		(fund* or financ*).ti,ab. and drug$.mp.	95,705
#4		risk shar*.mp.	781
#5		#1 OR #2 OR #3 OR #4	154,433
#6	High cost drugs	high cost$.mp.	124,488
#7		exp pharmaceutical care/	18,607
#8		gene therapy.mp. or gene therapy/	84,584
#9		cancer immunotherapy/ or cell therapy.mp. or cell therapy/	82,647
#10		tissue therapy.mp. or biological therapy/	11,314
#11		#6 OR #7 OR #8 OR #9 OR #10	202,510
#12	Final	#5 AND #11	3,759

2.1.5. Study selection

2.1.5.1. Inclusion and exclusion criteria

Inclusion criteria were:

- French/English language,
- 2010 <Study date < February 2017,

- The topic is financing new high cost drugs or innovative drugs.

Studies where no financing model for innovation was suggested were excluded from this review.

2.1.5.2. Titles and abstracts review

After validation and run of the search strategies presented in the previous section, references were imported into a reference manager database: Endnote X7. Duplicates were removed using Endnote X7 and then data was exported to an Excel sheet (Excel 2010) and the titles and abstracts were screened. The list of titles and abstracts was screened by one reviewer to select relevant articles, pertaining to the topic of interest according to the defined inclusion and exclusion criteria. References were categorized into Included or Excluded.

2.1.5.3. Full paper review

For any article that meets the inclusion criteria or could not be excluded based on the abstract review, the full text was screened to decide on inclusion or exclusion.

2.1.5.4. Inventory

All references identified by the search, and the different screening phases were recorded in an Excel file. This file, called the inventory, serves as a tracker of the above described steps.

Finally, when the selection of articles had been completed, a description of the selection process was provided using a PRISMA chart, including the number of selected publications at each step.

2.1.6. Data extraction: definition, advantages and limitations

The references that have been classified as “included” after full text screening were then extracted for relevant information in a table designed using Excel 2010.

The following data were extracted from the included articles:

1. Title,
2. Authors,

3. Journal,
4. Year of publication,
5. The new funding model suggested,
6. Definition and explanation on how this suggested funding model will work,
7. Advantages of the suggested model(s),
8. Limitations of the suggested model(s).

2.2. Classification

Funding models were classified into categories and subcategories based on the nature of agreements:

- Health outcomes based agreements

Agreements where the cost of the drug depends on the health outcomes provided by the therapy, as determined after launch in the "real world" clinical setting. Those schemes have a direct link between the outcome and the cost at an individual patient level or population level.

- Financial agreements

Financial-based agreements often involve setting limits on the price of a novel therapy or the volume sold.

2.3. Comparison

A consensus meeting was organized to identify, evaluate and compare the funding models features: the feasibility, acceptability, burden, financial attractiveness, appeal to payers, and appeal to manufacturer. The participants of the consensus meeting were:

- Two academic experts: Pr Mondher Toumi and Pr Pascal Auquier,
- One hospital pharmacist: Dr Claude Dussart,
- One former payer: Dr Borislav Borissov,
- One pharmaceutical industry director responsible for pricing: Dr Omar Dabbous,
- Two experts consultants working in the area for of pricing and market access: Ms Cécile Rémuzat and Mr Isaac Odeyemi.

Two charts were constructed using Microsoft Excel® 2010 to distribute the models based on their feasibility and financial attractiveness in the first chart and based on the appeal to manufacturer and payer in the second chart. In addition, the applicability of the models to different disease types of diseases was evaluated: chronic progressive

disease (e.g. Parkinson, Alzheimer), chronic disease with exacerbations (e.g. asthma), acute disease (e.g. acute leukemia) and organ defects (e.g. cartilage defect).

2.4. Discussion

This step involves reviewing the appropriateness of different models identified previously to be applied for ATMPs. We assessed and discussed the appropriateness of each model to fund ATMPs based on all the information collected through the literature review.

2.5. Recommendation

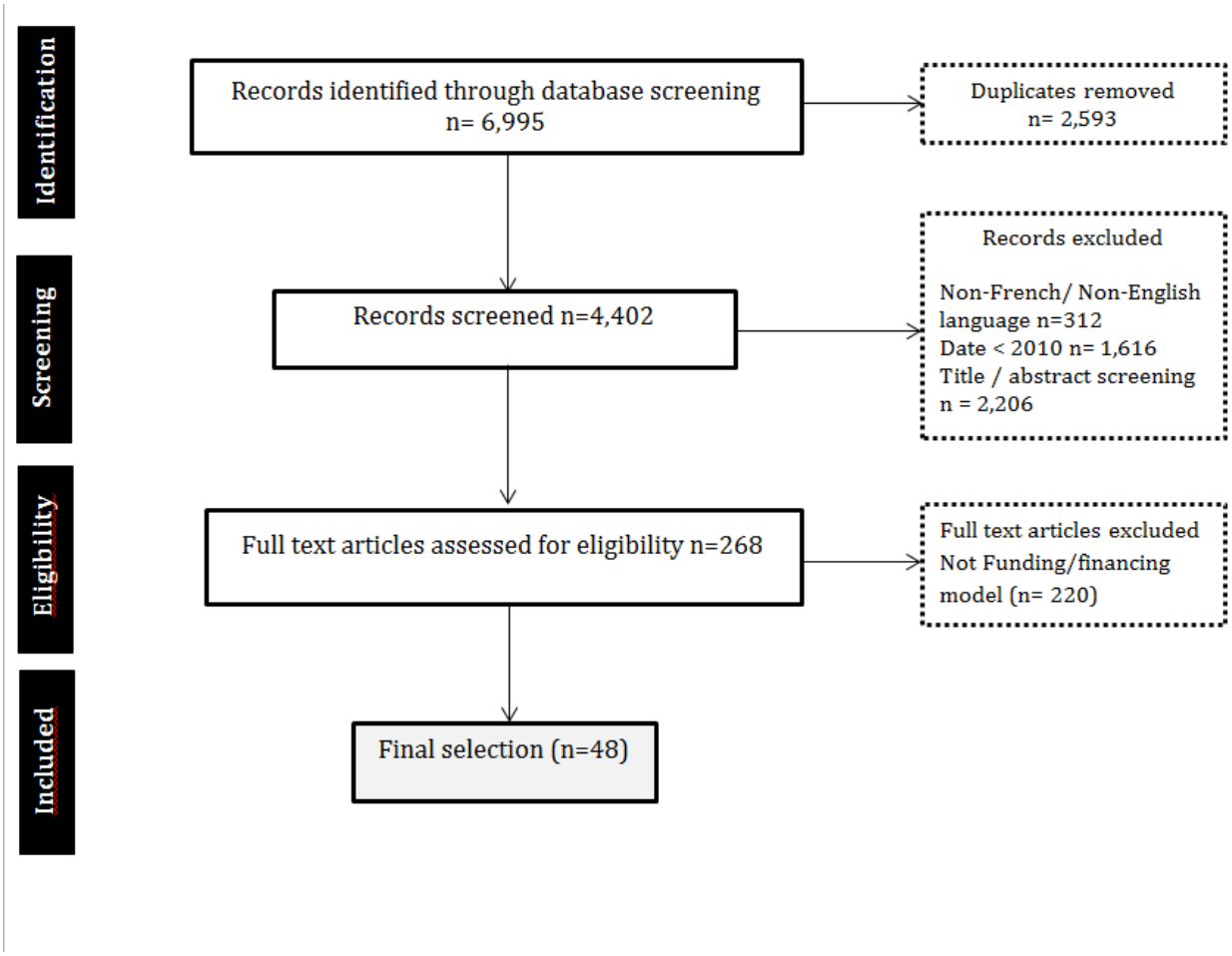
At the end of this chapter and based on all information extracted and assessed, an optimal funding model for ATMPs will be recommended.

3. Results

3.1. Identification, definition and classification of funding models

Overall, 6,995 papers were extracted from the keyword search in Ovid Medline, Embase and grey literature, among which 268 articles were eligible for full text screening. Forty-eight articles proposing methods of paying for high cost therapies were identified. The PRISMA diagram of search is presented in **Figure 40**.

Figure 40. PRISMA diagram of search



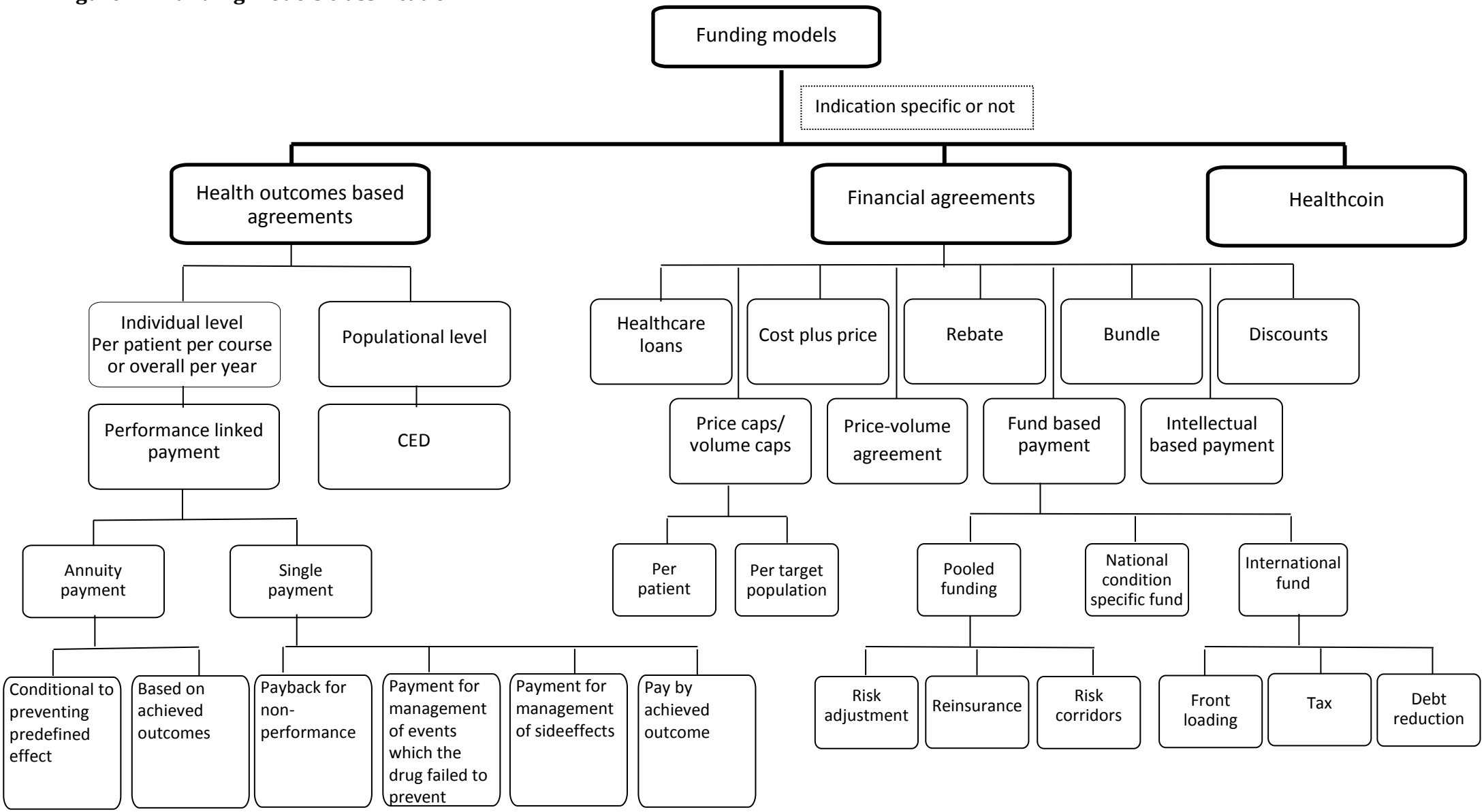
The funding models identified were classified in 3 categories: financial-based agreements, health outcomes based agreements, and healthcoin (Figure 41).

Funding models may be indication specific or not linked to the indication.

Health outcomes based agreements were divided into coverage with evidence development (CED) at population level and performance linked agreement at individual patient level, it can be an agreement per patient, per course or per year of treatment. Performance linked agreement can be single payment or annuity payment. Annuity payment consists on spreading the cost of a therapy based on achieved outcomes or prevented effect. Single payment can be a payback for non-performance, payment for management of events which the drug failed to prevent, payment for management of undesirable effects and pay by achieved outcome.

Financial agreements encompass the healthcare loans, Cost plus price, discounts, rebates, bundle payment, Price-volume agreement, Price caps/ volume caps per patient or per target population, intellectual based payment and fund based payment that includes pooled funding, national silo funds for specific conditions and international funds.

Figure 41. Funding models classification



3.1.1. Financial agreements

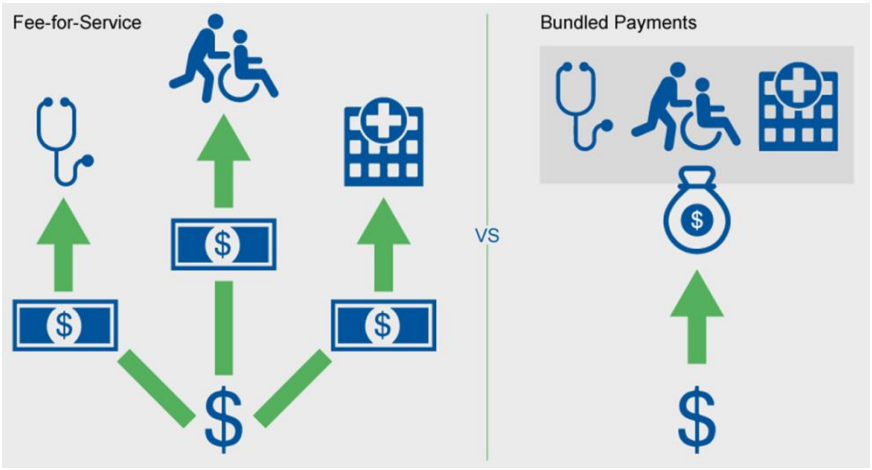
Several financial agreements were proposed in 30 articles. These agreements between payers and manufacturers were based only on financial aspects and were independent of health outcomes of the novel therapy. The financial agreements identified were grouped as follows:

3.1.1.1. Bundle payment, episode of care

An episode of care is a single payment for all clinically related services for one patient for a predefined discrete diagnostic condition. It is characterized by events defining the start and end dates (297, 298). For acute conditions (e.g. bone fracture) the episode starts from the onset of the condition and ends at its resolution or symptoms disappear. For chronic conditions (e.g. Parkinson), the episode refers to all services and treatments received over a given period of time, commonly one year. One episode only pertains to one patient, however one patient can be in multiple episodes at once.

A bundle payment is an integrated single payment that covers all healthcare services related to a specific treatment, or procedure (297-304) instead of paying for every service provided (Figure 42). Healthcare providers will not be paid for additional services therefore better coordination is encouraged.

Figure 42. Bundled payment concept



Difference between fee-for-service on the left and bundled payment on the right. Figure from NAHU Education Foundation (305).

The aim is to incentive health care provider to control drug expenditure while maintaining the quality of care monitored through predefined quality metrics.

Episode of care and bundle payments can yield savings in three ways: 1) price negotiation so the total cost will be less than fee-for-service; 2) agreement with providers that any savings that arise will be shared with them; 3) savings because no additional payments will be made to treating complications of care.

This is also the principle of an integrated health system, where health care providers create a joint organization to deliver comprehensive care for patients with a given condition. In the US, integrated systems were promoted by Obamacare (the Patient Protection and Affordable Care Act) and are called Affordable Care Organizations (ACO).

For cancer care, a new model of ACO – the Oncology Care Model (OCM) – was developed by Centers for Medicare & Medicaid Services (CMS). It is an episode based model, the total cost includes chemotherapy treatmenbnt and all medical services during the following 6 months.

In addition to the fee-for-service payment for each episode of oncology care, the model includes two further payments (306):

- Funding for enhanced care management services : per-beneficiary per-month (PBPM) fee for each episode of chemotherapy (160$),
- Performance-based payment: it is a semi-annual lump sum . It depends on satisfactory quality metrics and spending per chemotherapy episode falling below a predefined target.

3.1.1.2. Rebates (307, 308)

Payments refunded by the manufacturer to the payer after the transaction has occurred. This commercial agreement, usually confidential, is becoming increasingly popular in several countries. It may be driven by the Incremental cost-effectiveness ratio (ICER) or result simply from a negotiation with no objective economic evidence to match the affordability or willingness-to-pay subjectively defined by the payer.

3.1.1.3. Discounts (309-311)

Price reductions granted to payers under specific conditions. It is a simple discount on the unit price of a drug. They are usually confidential, and do not affect the list price of

the drug. Discounts can vary widely, but most commonly the discount is over 20% of the list price (312). Confidential discounts are now common in Europe.

3.1.1.4. Price caps/volume cap per patients or per target population (307, 308, 313)

Price caps and volume caps are methods used to control and limit pharmaceuticals prices and manufacturers revenues.

- At patient level, they aim at capping the yearly price or the number of yearly treatment courses reimbursed. If additional courses are needed, these have to be provided by the manufacturer free of charge.

- At population level, these strategies aim at capping the yearly expenditure/volume the manufacturer will be allowed to sell. Beyond the cap, manufacturer may have to reimburse the full retail price, the full ex-factory price, or a proportion of the price, depending on the details of the agreement.

Levy et al. (313) suggested a model that provides a theoretical foundation for price caps to face the monopolistic power of pharmaceutical companies. A mild price regulation (a 20% decrease) was considered the "golden path" to improving patient health without stifling the incentive for innovation (313).

3.1.1.5. Price volume agreements (308, 314-316)

Agreements where drug prices are reduced based on sales volume. For example, after selling 10,000 vials, the price is reduced by 20% for the next vials and so on. Alternatively, depending on the total sales volume, the price will be discounted for all vials sold, according to a predefined scheme.

3.1.1.6. Cost-plus price (317, 318)

Cost-plus price or also called cost-based price consists on pricing the drug based on the cost of this drug instead of its value. It has been proposed for orphan drugs that are generally not considered cost-effective due to their high costs. For example, it was argued that Gilead should be compensated by a prize of US$5bn for the development of sofosbuvir that costed it around US$500M (294).

However, cost-based price may incentivize companies to invest in innovative drugs with little value and high cost of development.

Two methods were reviewed by Fellows GK and Hollis A (317): The rate of return (ROR) and yardstick regulation.

- Yardstick regulation consists on using a comparative pricing mechanism where the price of the new drug is based oin the cost incurred by other firms to the production of a similar product. This method is usually used when several firms operate in the same market.

- In the ROR, the price is set at a level that produces total revenues equal to a fixed and pre-determined amount. It aims to compensate the costs incurred by the firm and ensure a fair return on investment. Regulated prices are set for a predertermined period. After this period, the price is reviewed. The "rate of return" method helps to determine a "just and reasonable price" for the orphan drug (317).

Persson et al. (318) suggested splitting pharmaceuticals costs in Sweden between two payers: regional and national, resulting in a combination of value-based pricing for innovation at national level with cost-plus pricing at regional level.

3.1.1.7. Drug mortgages, Healthcare loans (319)/ credits (320-322)

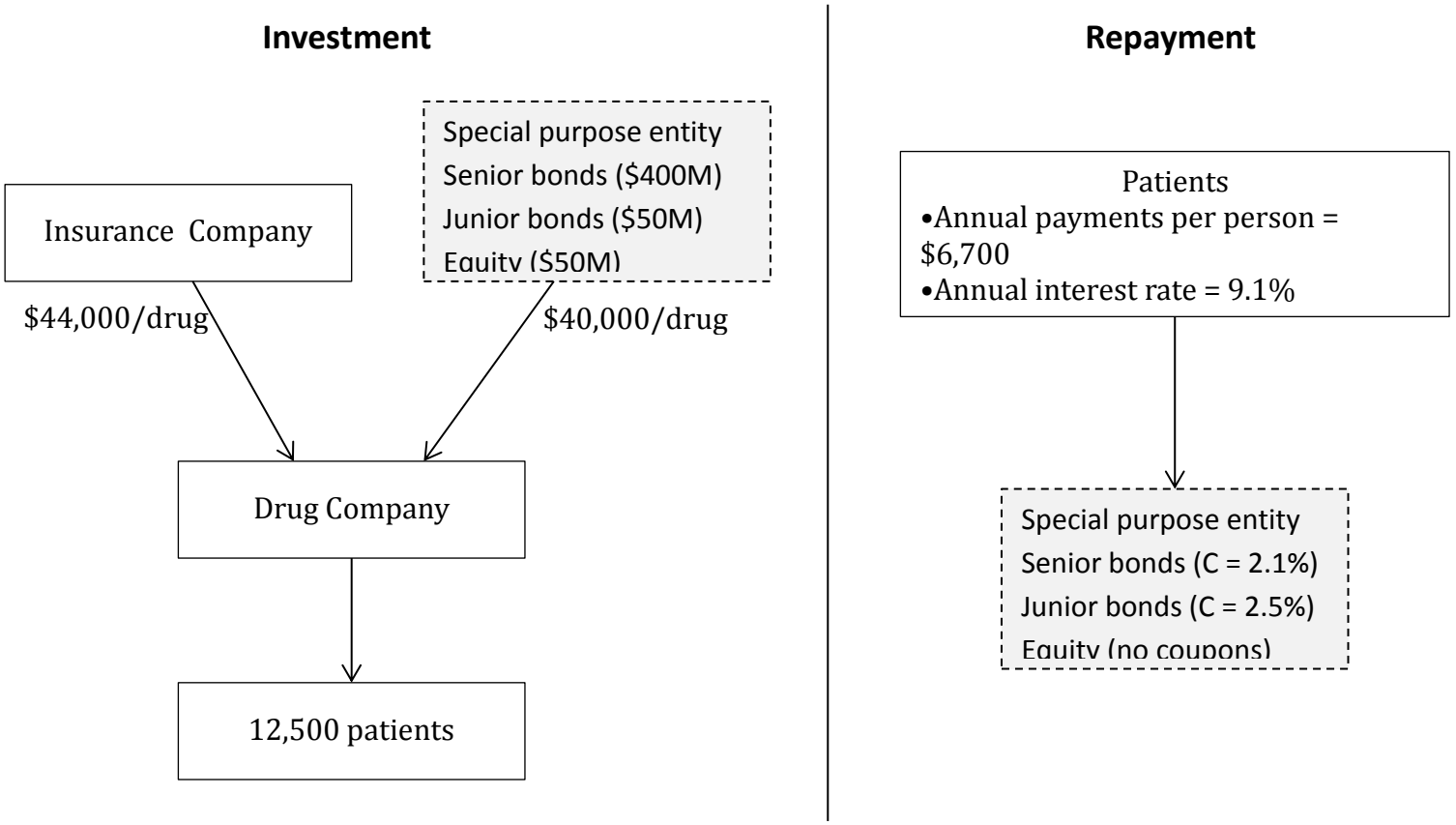
Drug mortgages spread the cost of treatments over many years instead of paying the whole price upfront. Other proposed methods with the same aim are: credits (320-322), healthcare loans (HCL) (319). Two frameworks are possible; credits can be allocated to payers or patients.

- In the first framework, patients borrow money from a specific entity to pay their copayments. The loan is then amortized over a predefined periods . It is the same concept like credit cards or student loans. The specific entity in this case may be from a pool of investors. Figure 43 shows the cash flow from investors to patients and from the patients to investors in the repayment period (319).

- In the second framework, private and public payers assume the debt.

They allow overcoming the financial liquidity limitation and increasing affordability. However, credits do not incentivize companies to lower the high-cost of the drugs. Furthermore, payers credits will increase the demand for the new drug which will ibncrease the burden on payers.

Figure 43. Cash-flow proposed by Montazerhodjat V et al. (319)



3.1.1.8. Fund based payment (323) divided in 3 subcategories: pooled funding (301, 320, 324-326), national silo funds (327-329), and special international fund raising (324)

Reinsurance risk pool

Pooled funding through the reinsurance risk pool of multiple payers (325) is a way to secure high costs of drug treatment for an individual outlier patient. Such insurance may apply to public-private partnerships that aim to recover the costs of goods within a given time period through the collaboration between public and private payers (301, 324, 326). Zettler et al. (320) proposed the 3Rs method: 1) risk adjustment is a fund collected from all payers that aims to compensate payers that incur unusually high costs, 2) reinsurance is an insurance policy that insurers buy to protect against excess

financial risk and 3) risk corridors method where U.S. Department of Health and Human Services (HHS) collects funds from plans with lower than expected claims and makes payments to plans with higher than expected.

National silo funds

National funds for specific conditions or diseases: for example the Cancer Drug Fund (CDF) in the United Kingdom that pays for new cancer drugs rejected by NICE (327, 328) and Australian complex Authority Required Highly Specialized Drugs Program that funds and delivers specialty drugs (329).

Special international fund raising

Three international financing methods addressing non-communicable diseases were identified (324):

1) international taxes on specific transactions that will be used to finance some drugs procurements and supply (e.g. airline tax levy),

2) frontloading of aids from donors to invest in health programs or drugs (e.g. funds received by the International Finance Facility for Immunization), these methods can ensure sustained and predictable annual funding

3) debt reduction where the creditor country writes off debt for a low- and middle-income country with the commitment of the latter to invest in a domestic therapy or prevention program, this method is a one-time transaction, unlikely to provide stable funding.

3.1.1.9. Intellectual based payment (323)

This approach includes prizes for patents – public payers buy the therapy from the manufacturer and gain control over its production and distribution. The approach may also involve out-licensing production and distribution to payers, with the manufacturer maintaining their intellectual property (IP) rights. Furthermore, prolonging patent rights – as with orphan drugs – rewards innovation. In Europe, orphan drugs benefit from a market exclusivity of 10 years after the marketing authorisation, in addition to the data exclusivity.

Fund-based payments and intellectual-based payment were proposed by Carr et al. (323) to pay for gene therapies.

The detailed definition with the advantages and limitations of each method are presented in Table 42.

Table 42. Identified funding models based on financial agreements: definition, advantages and limitations

Method	Definition	Advantages	Limitations	Reference
Bundle	An all-inclusive payment per enrollee for a defined scope of services, regardless of how much care is provided. Integrate payment and reward for all services related to a specific treatment, condition or individual; by procedure or episode of care, by condition-specific capitation, or by global capitation	-Core tools for advancing value-based health care -Transfer the financial risks and rewards of patient care to health care providers -Allow better predictability of budget spending - Can yield savings for payers	Health care provider may limit the adoption of innovative therapies to maximize their margin	Korda H et al., 2011 (299) Robinson JC, 2013 (300) Hussey PS et al., 2011 (298) Jain S et al., 2014 (301) Barinaga G et al., 2016 (297) Licking E et al., 2016 (302) Greenapple, 2013 (303)
Episode of care	Payment of a single sum for all the care a patient needs over the course of a defined episode of care instead of paying for each discrete service	Improved quality of care and decreased economic burden Allow better predictability of budget spending	Paying for discrete episode might not control the total number of episodes and could encourage more episodes Feasibility concerns and implementation challenges	Barinaga G et al., 2016 (297) Hussey PS et al., 2011 (298)
Rebates	Payments refunded by the manufacturer to the payer driven by the Incremental cost-effectiveness ratio (ICER) or simply determined during a negotiation	Confidential Ensures savings	May distort external reference pricing	Gavious A et al., 2014 (307) Jarosławski S et al. 2011 (308)
Discounts	Confidential discounts for payers	-The most relevant	- May be difficult to keep	Anastasaki E et al., 2011 (309)

		solution for payers - May be simple, depending on pricing	confidential	Aggarwal S et al., 2013 (311)
Credits (Payers level)	-Governments facilitate better credit instruments for public payers -Credit or contracting arrangements between payers and pharmaceutical companies	Amortizing the cost of treatment by purchasing drugs without paying the entire price up front	Pharmaceutical companies may want to gain immediate revenue to boost their return on investment Will eat into future revenue and reduce future affordability to payers	Philipson T et al., 2014 (321) Gottlieb S et al., (322)
Healthcare loans (HCL) for patients (Hybrid models)	- An equivalent of mortgages for large health care expenses - Credit vehicles (e.g. Credit cards) which allow patients to smooth out-of-pocket costs over time. Interest rates can be reduced	Increase drug affordability	Publicly available data on student loans and other consumer financing might not fully capture the risks of HCLs Additional mechanisms to improve feasibility of third-party borrowing by patients' family members, for example Will eat into future revenue and reduce future affordability to payers	Montazerhodjat V et al., 2016 (319) Philipson T et al., 2014 (321)
Cost based price	Cost-based mechanism proposed for treatment of rare diseases that are not cost-effective, in order to determine a "fair and reasonable price": Yardstick regulation: comparative mechanism in which	-Yardstick : direct competition between firms , incentives for firms to reduce costs -Rate of return (ROR): determination	-Yardstick is difficult to apply if there are no or few companies producing similar products -ROR: disagreement between regulator and	Fellows GK et al., 2013 (317)

	the regulator uses this mechanism to set a regulated price for a drug based on the costs incurred by similar companies producing the same good Rate of return (ROR): price is set such that it produces total manufacturer revenues that are equal to a fixed and pre-determined amount, referred to as the "revenue requirement"	of a fair price	the company on the costs used to calculate the rate -Price not linked to "value", resulting in a disincentive to develop better products	
VBP plus free market pricing	Splitting the cost between regional and national payers: the local councils pay the marginal cost of production (cost-based price) while the state pays for the innovation. The county councils pay the 'cost-plus' price (Px), that is lower than the price company demands PVBP, [(PVBP-PX)* QVBP] is divided by the number of patients in the indication. The quotient is paid by the state. The quotient plus the cost-plus price is the price on the Swedish market.	Increase affordability by sharing costs between multiple stakeholders	Administrational burden affects two different payers, and the process involves setting two different types of prices Does not reduce the burden to the society, even though different public bodies share the cost	Persson U et al., 2012 (318)
Price caps (mild regulation)	An optimal monopolistic price determined by the company serves as the basis for price regulation. The model provides a theoretical foundation and benchmark for setting price caps (mild regulation e.g. 20% lower than optimal monopolistic price)	-Increase in consumer surplus and in the number of patients with only a marginal effect on the revenues of the company - Patient welfare improvement - Do not stifle the economic incentive for	Direct negotiation may bring a significantly lower price for payers	Levy M et al ., 2014 (313)

		drug innovation.		
Price volume	-Nation-wide budget thresholds for individual innovative agents: the price is reduced when the number of patients receiving the drug increase - The basic parameter of the model is represented by the price halving population (PHP) according to which the treatment price is halved at every increase in the number of treated patients equal to the PHP.	Promoting sustainability	Complex to break down into various subtypes of costs	Messori A, 2016 (314) Barry M et al.,2010 (330) Toumi M et al., 2013 (316)
Fund based payment	-National silo fund for specialist conditions (e.g. Cancer Drugs Fund) -Social funds financed by private companies and/or insurers	Attractive, as funding is secured for conditions that are covered	National healthcare providers and insurers are unlikely to risk such a high level of investment for unproven drugs	Carr D et al., 2016 (323)
Intellectual based payment	-Prizes for patents: public buy-out of the therapy, rewarding the manufacturer with a financial sum in return for full government control over production and distribution -Out-licensing of technology rights: license out production and distribution rights to public or private payers, while the manufacturer maintains intellectual property (IP) rights -Prolonged patent rights: marketing exclusivity extension , as in the case of orphan drugs	-Reward and incentivize innovation -Manufacturer no longer needs to seek high prices for treatment	-Do not reduce the uncertainty -Neither attractive to manufacturers or payers as interests become reversed (payers become responsible for production, amongst others), while the risk of monopolization can have impact on innovation over time	Carr D et al., 2016 (323) Jain S et al., 2014 (301)

Pooled funding	**Public/private partnerships** : funding from multiple groups is combined for a specific investment purpose. Collaboration between public and private payers that aims to recover the costs of community goods and services – medical and pharmaceutical services, equipment, insurance, social security –within a given time period **Reinsurance risk pool:** the high aggregate costs of drug treatment for an individual patient are borne by a risk pool of multiple payers. This pool reimburses payers for the portion of claims incurred by high-cost patients, the same way reinsurance does now for very high-cost healthcare claimants in general	Spread the cost over everyone in the insurance pool rather than imposing an unreasonable financial burden on the patient	Lack of integration of monitoring structures with other donor initiatives	Jain S et al., 2014 (301) Meghani A et al., 2015 (324) Beauliere A et al., 2010 (326) Kleinke JD et al., 2015 (325)
Levies	International transactions taxes or levies placed on a specific transaction for the purpose of supporting health programs, including investments in drug procurement and supply in low- and middle-income countries.	Provide sustained funding	Airline ticket levy Would affect the volume of airline travel dissipated	Meghani A et al., 2015 (324)
Front-loading	Frontloading of foreseeable donor aid into resources immediately available for health programs through bond issues backed by donor pledges	Predictable annual funding	3.5% interest rate and associated commission fees linked with the bond sales	

Debt Reduction	A creditor agrees to write off debt for a recipient country if the recipient commits counterpart funding to an account that had been approved for domestic programs through a review process	Ensure fund	Limited impact in low and middle-income countries with low external debt -No recurrent long-term, stable funding because often one-time transactions.	
3Rs	**Risk adjustment program**: all payers pay into a fund that will compensate those payers that incur unusually high costs. **Reinsurance** is an insurance policy that insurers buy to protect against excess financial risk. **Risk corridors** U.S. Department of Health and Human Services (HHS) collects funds from plans with lower than expected claims and makes payments to plans with higher than expected claims. Plans with actual claims less than 97% of target amounts pay into the program and plans with claims greater than 103% of target amounts receive funds.	Protect insurers against adverse selection and consumers against destabilization of the insurance market and discriminatory health insurance practices **Risk corridors** limit both downside risk of losses and excess profits for health plans	Political and legal Challenges	Zettler et al., 2017 (320) Proach J et al., 2016 (331)
Cancer drug fund	Created in 2010 by the coalition Government to pay for new cancer drugs that National Institute for Health and Care Excellence (NICE) considered they were not cost effective.	Pay for new cancer drugs rejected by NICE	Onco-exceptionalism, inefficient, no discounts	Jack A, 2014 (327) Mayor S, 2016 (328)
Australian complex Authority Required Highly	Created to fund and deliver specialty drugs. Patients must show clinical need and adequate clinical	Balance the benefits, risks, and costs	-	Lu CY, 2012 (329)

Specialized Drugs Program	improvement to continue to receive the drug in this scheme

3.1.2. Health outcomes based agreements

This class encompasses agreements between manufacturers and payers based on drug performance. It is divided in two groups: individual level performance based payment and population level conditional reimbursement often called coverage with evidence development (CED).

Individual level performance-based payment is further split based on payment frequency – it can be an annuity or a single payment.
"Pay-for-performance" (P4P) is a solution to pay for innovative high cost therapies proposed in fifteen studies (296, 308, 311, 330, 332-343). Towse's definition of performance-based agreement (296) is an agreement between payer and manufacturer where "*the price level and/or revenue received is related to the future performance of the product in either a research or a real-world environment."*

P4P encompasses several types of agreements: payback for non-performance, payment for management of events which the drug failed to prevent, payment for managing undesirable effects, payment for achieved outcome etc. (339). In the latter agreement type, each treatment is considered either a success or a failure, based on a predefined outcome measure (e.g., disease progression) and a predefined timing of outcome assessment (e.g., 6 months). P4P agreements ensure market access for innovative promising therapies, demonstrate value, allow sharing the risk between payers and manufacturers, and limit total budget impact. However, they require logistics and bureaucracy that are associated with additional costs and increase manufacturer and healthcare provider burden. In addition, there is no guarantee that the product will retain its market position after re-assessment; reimbursement discontinuation or price-cut are also possible options.

Another suggested method was linking the price to the indication: indication specific pricing (302, 344). It may be used like in Italy with a price per patient and per indication based on differential managed entry agreement per indication. This model is, however, resource-consuming. The alternative is to use volume-weighted average of the differential prices per indication. In this case, the weights are initially speculative and

the payer requests that they are confirmed in a real world study, such as a database analysis (344). As a result of the indication-specific pricing approach, manufacturers are rewarded for their drugs being more effective. This prevents manufacturers from focusing only on high-benefit indications to maintain a high price.

Rebate risk sharing proposed by Kleinke et al.(325) consists of rebates to patients with large cost-sharing after the completion of milestones or course treatment. This method can improve patients' adherence as the adherence to the treatment will be rewarded by the rebate.

A limit pricing approach based on health outcomes similar to NICE threshold was proposed by Fuller & Goldfield (337). It includes in the calculation the payment for outcomes such as avoided hospitalizations and outcomes as decreased mortality not easily translated in dollars. Not met performance milestones would convert into price reductions.

"Annuity style payment" (323), "annuity with risk sharing" (345), "technology leasing reimbursement scheme" (346) and "high-cost drugs mortgages" (325) are terms used in several articles to describe the agreement between manufacturers and payers aiming to replace the high upfront cost with a stream of payments triggered, at patient level, by the achievement of clinical milestones. However, an important challenge lies in defining the clinical milestones and endpoints, which may be critical.

Coverage with evidence development (CED) is also a method suggested in 4 papers (296, 316, 340, 347). It is a conditional reimbursement linked to the collect of post-launch real world data. Once that data is available, a price re-negotiation occurs if the product does not meet the expectations. However, in most cases, there are no prior agreements on the interpretation of evidence and price revisions based on the evidence generated by manufacturers. A CED scheme may be complemented with an escrow agreement. The escrow agreement places the sales revenue in an independent bank account; at the end of the study, the collected money is released to the company if the results are positive and to the health insurance if the results are negative.

3.1.3. Healthcoin

Basu et al. (348), suggested a new tradable currency "Healthcoin" as a financing mechanism for breakthrough therapies. It converts the incremental outcomes produced by curative treatments to a common numeraire, such as lifeyears equivalents. It can be

traded to dollars in the marketplace. Medicare would pay the private payer for a beneficiary who is transitioning to Medicare at the age of 65 years, if the private payer had previously invested in a cure for diabetes for example. Healthcoin incentivizes private payers to invest in breakthrough treatments, especially in curative therapies that are in demand in non-elderly. The model limitation is the assumption that the cure is permanent and applies equally to all ages.

3.2. Comparison of the proposed funding models features

Table 43 shows the funding model features: feasibility, acceptability, burden, financial attractiveness, appeal to payers and appeal to manufacturer. Most of the models were considered feasible. The least feasible and acceptable ones were: credits for patients, cost plus pricing, intellectual based payment, pooled funding, international funds, and healthcoin. Almost all of the funding models are associated with additional burden, except for rebates, discounts, price caps, and price–volume agreements. All models except intellectual based funding could be considered appealing for payers and the models most appealing for manufacturers were: credits/ HCL, national silo funds, international funds, CED.

Table 43. Funding models features

Funding model	Feasibility	Acceptability	Burden	Financial interest	Appeal (payers)	Appeal (manufacturer)
Financial based funding						
Bundle payment/ Episode of care	+++	+++	+	++	+++	++
Rebates/ Discounts	+++	+++	×	+++	+++	++
Price caps/volume caps	+++	+++	×	+++	+++	+
Price – volume agreements	+++	+++	×	+++	+++	++
Credits for patients	+	×	++	+++	+	+++
Healthcare loans for payers	++	++	++	+++	+	+++
Cost based price	+	×	++	+	+++	×
National silo	+++	++	+	+++	+++	+++

fund (e.g. CDF)						
Intellectual based payment	+	×	+++	+	+	×
Pooled funding	+	+	++	+++	+++	+++
3Rs	++	+	++	+++	+++	+++
International funds	++	+	++	+++	++	+++
Health outcomes based funding						
Coverage with evidence development	+++	+++	+++	++	+++	+++
Pay for performance	+++	+++	+++	+++	+++	++
Annuity payment based on performance	+++	+++	+++	+++	+++	++
Healthcoin	+	×	+++	++	+	+

+: Low importance, ++: Important, +++: Very important, ×: No

Figure 44 shows that annuity payment, P4P, discounts/ rebates and national condition specific funds are the top 4 funding models based on the feasibility and financial interest.

Figure 44. Matrix for the feasibility and financial interest of each funding model

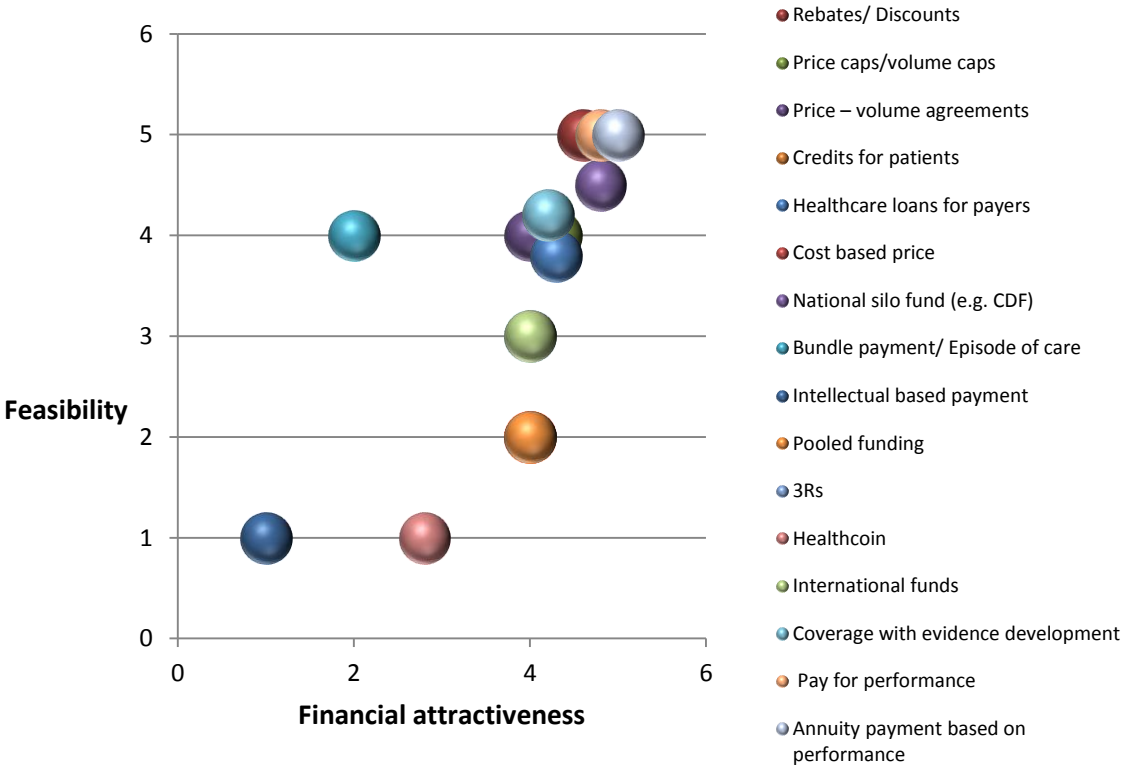
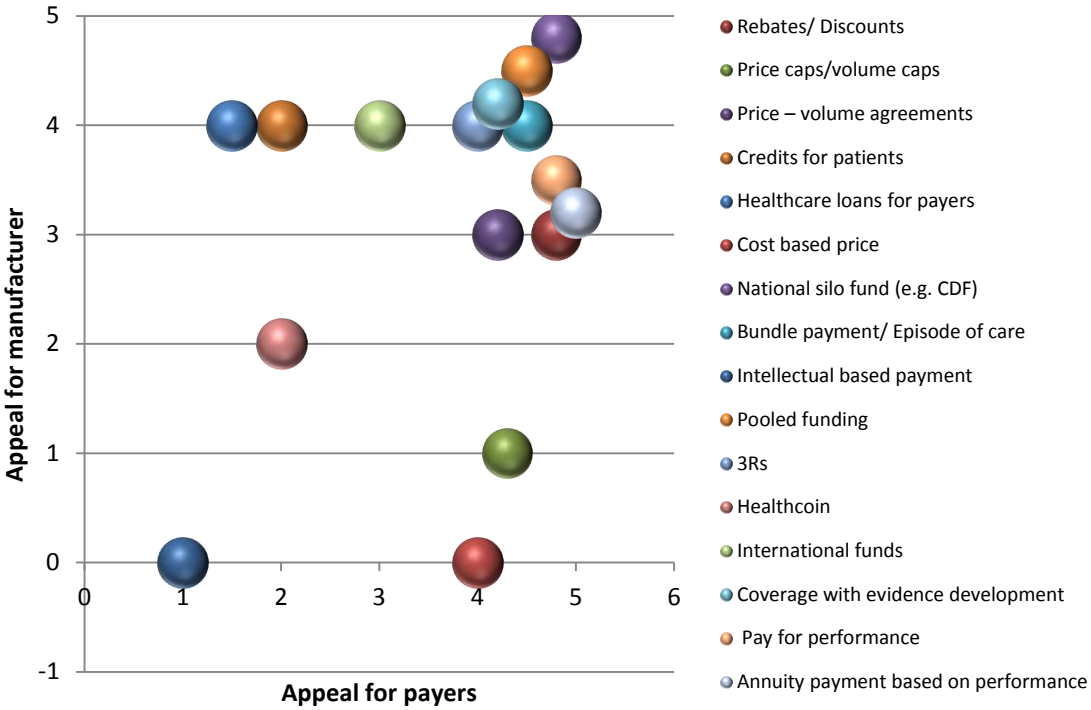


Figure 45 shows that national silo funds are the most appealing for both manufacturer and payers.

Figure 45. Matrix for the appeal for payers and manufacturer of each funding model



Funding models are generally adapted for all diseases types: chronic progressive disease or with exacerbation, acute disease, and organ defects. There are some exceptions described in Table 44.

Table 44. Type of diseases for each funding model

Funding model	Chronic disease slow progression	Chronic disease with exacerbation	Severe disease	Organ defect
Financial based funding				
Bundle payment/ Episode of care	×	✓	✓	✓
Rebates/ Discounts	✓	✓	✓	✓
Price caps/volume caps	✓	✓	✓	✓
Price – volume agreements	✓	✓	✓	✓
Credits for patients	✓	✓	✓	✓
Healthcare loans for payers	✓	✓	✓	✓
Cost based price	✓	✓	✓	✓
National silo fund (e.g. CDF)	✓	✓	✓	✓

Intellectual based payment	✓	✓	✓	✓
Pooled funding	✓	✓	✓	✓
3Rs	✓	✓	✓	✓
International fund	✓	✓	✓	✓
Health outcomes based funding				
Coverage with evidence development	✓	✓	✓	✓
Pay for performance	×	✓	×	×
Annuity payment based on performance	✓	✓	×	×
Healthcoin	✓	✓	✓	✓

✓: applicable
×: not applicable

4. Discussion

The concept of "curative" therapies is getting close to reality, with the large number of ATMPs in development (162). Questions on the adoption of these therapies, and on the means through which healthcare payers can finance them, are being raised increasingly often. A specific financing issue differentiates potentially curative therapies like ATMPs from other pharmaceuticals; it is the high upfront costs with downstream outcomes. These high upfront costs will likely threaten the sustainability of the health care system, and balancing innovation and affordability may become a challenge for payers. As a result, new financing models are needed to guide decision making. Among the 48 papers included, gene therapy funding was the topic of only 3 papers, and no papers discussed funding for cell therapies and tissue-engineered products. This confirms our hypothesis that payers need guidance that will help them put together a strategy to ensure funding for ATMPs.

In this chapter, proposed approaches to funding innovative high-cost medicines were identified, defined, classified and compared. In the next sections, the appropriateness of these models for ATMPs funding will be analyzed and an optimal ATMP funding model will be suggested.

Proposed payment models for innovative breakthrough therapies were mainly performance based agreements and financial based agreements with advantages and limitations in solving the challenge of adopting high cost innovative therapies. Some of

the proposed funding models are already used in Europe or the United States (US) and several other countries, others are emerging.

Among the proposed approaches, the cost-based pricing (317) may be the least acceptable strategy. This method allows reasonable profit for manufacturers but the price is not linked to the product value. It may improve access to ATMP only if the new price set by this method is lower than the price set through traditional methods. It may then be seen as a disincentive. In fact, this model is designed to reward investment in products such as orphan drugs which may not be profitable without such incentive.

The CED appears to be the right tool to address uncertainty but not the affordability. In addition it may fail to capture the needed data to reduce the decision making uncertainty thus the agreement may be terminated (55). CED of orphan drugs experience in the Netherlands was not favorable; some drugs were not proven cost-effective but it was impossible to stop coverage due to public pressure (349).

In some circumstances where payers cannot clearly identify the source of uncertainties, an individual P4P may be the solution. They are not cost-containment tools, they do not address affordability. Payers are increasingly experimenting P4P schemes (334). This solution should be an exception because it does not address the actual uncertainty and is resource consuming; tracking the therapy value over time requires logistics, metrics and registries therefore additional burden for manufacturers or payers. P4P agreements may have a place in ATMP funding but their role will be addressing payers' uncertainties rather than budget constraints challenges. CED should be preferred whenever possible.

Aidan Hollis has put in place an alternative mechanism close to pay for performance mechanism, called "Health Impact Fund" (HIF). By registering the drug under this fund, the pharmaceutical company accepts to sell the drug globally at cost, without diminishing patents rights. In exchange, the HIF distribute to the companies an additional amount of money calculated based on the health impact of each product each year (350).

Some funding models aimed to transfer the drug budget responsibility to healthcare providers with an opportunity for payers to avoid negotiating prices. Prices are discussed between manufacturers and healthcare providers. The most known model using the same concept is the hospital payment by Diagnosis-related group (DRG), and bundle payment with a procedure. This is also the objective of funding process of ACO,

or OCM or episode of care. The payer shifts the financial risk to healthcare providers and creates incentives for budget control by providers. Performance criteria may be part of the quality metrics used by payers to create incentives for outcomes optimization. One of the limitations of this type of payment model is that when novel innovative potentially expensive therapies become available there is a need for a temporary funding on the top of the pre-defined payment. Usually such payments are covered by a central budget envelop. This may be an incentive to use expensive products funded by a side budget envelop. It will not be attractive or feasible in countries where changes of insurers or treating physicians are frequent like in US. Under the provision that patients remain covered by the same insurer on a long run such payment models may prove to be useful for ATMP funding. Furthermore, an alternative solution would be to couple bundle payments with 3Rs or pooled funding options to overcome the switch between insurers or also adopting healthcoin model. Pooled funding and 3Rs are interesting funding routes to ensure fair cost share between payers. It may address payers' hesitancy to invest when the return on investment is built over a long period. Therefore, it may help adopting ATMPs in a fragmented volatile insurance market like US. However, pooled funding may reduce the incentive of manufacturers to reduce ATMPs targeted prices. In addition, attendees of ICER policy summit meeting stated that insurers are already trying to exclude gene therapies from reinsurance policies although a limited number of gene therapies is currently marketed (351). Healthcoin could be applied between private payers and Medicare or also between private payers when a patient switches from a plan to another. This will expand the possibility to invest in long term benefit despite patients possible plan switch after receiving the intervention.

The levies, front-loading and the debt reduction are alternative solutions that may be considered for low or medium income countries or countries affected by unmanageable debts that constraint dramatically their ability to invest in health. These methods are not specific to ATMP but may contribute to enhance ability to access to some specific ATMPs through international solidarity especially if associated to differential pricing. This is typically what is happening in Europe for all fields but health. It is hard to understand that such regulation is in place in EU for compensating agriculture products but is considered impossible for health services or innovative expensive products. Sustainable fund is critical, an initial funding needs to be associated to follow-up funding. The IP route seems inappropriate as the regulator will bear the production and distribution burden. In addition, if the government becomes the operator, the negotiation with the

pricing committee representing the government would be unhealthy. It may be more appropriate for the government to better protect IP emerging from academic and public research centers as more than 50% of drugs are built based on their discoveries. This funding process will unlikely be adopted by many liberal countries, moreover it may not enhance access to ATMPs.

Discounts and rebates aim to reduce the bill on the payers and thus adjust the net price to payers' affordability while maintaining the facial/listed price. These agreements will temporary be helpful in rich countries but it is unlikely to help middle and low income countries to access such products that are by far unaffordable for them.

Other models aim at controlling the budget expenses on a new product to ensure compatibility with payers' budget. It may apply at individual level by capping the reimbursed number of product administrations (e.g. 10 vials per year); the drug cost per patient is well identified or at population level by setting the total expenses for a product. The company is expected to limit the diffusion of the new technology to a subset of patients which may be driven by geography, specialist academic centers or any other criteria that ultimately increase inequity in access to healthcare. It is unlikely to be the right solution for ATMP as large diffusion to all eligible patients is the only ethically acceptable target.

Others aim to provide a price volume indexation. The price is an index on the achieved yearly volume of sales. Although not paying the same price for a larger or small volume of goods does make sense, it is unlikely to help making unaffordable prices affordable. Therefore it may only marginally help to ensure access to ATMP. It will create inequity against small countries.

The annuity payment may be considered as an attractive payment for ATMP because it spreads the upfront payment and link the payment to pre-defined health outcomes. This model seems the ideal solution as it addresses at the same time the high budget impact and the performance uncertainty. However, it should be seen as a loan and the delayed cost for payers is slowly cannibalizing the future health care budget. Annuity payment and payers credits may not necessarily be an actual good solution. In reality, they will ultimately book the future payers' budget and will challenge the sustainability of the health insurance unless future revenues are expected to increase significantly to cover the credit engaged for expensive products access or when the additional budget impact is considered as affordable by payers. The condition specific funds are abounded

through the government budget on the top of the health insurance budget through taxes. These funds allow circumventing affordability and the tight pricing regulation for pharmaceuticals creating an exception. It may represent an option to finance ATMP. Because ATMPs represent a high upfront cost, but associated with a very high clinical benefit on long-term, it seems reasonable that the government wants to invest in population health for long term benefit. This could be an excellent model for ATMP but difficult to put in place if as expected multiple ATMPs reach the market with outstanding benefit for patients and the society.

The experience of special funds was already adopted in several countries that have implemented special funds for orphan drugs. In Italy, a "5% AIFA fund" is collected from pharmaceutical companies and half of the fund is devoted to providing access to medicines for rare diseases before marketing authorization (352). In Scotland, "new medicines fund" (NMF) is implemented with £80M budget to ensure patients' access to end-of-life or orphan medicines while Health Boards are protected from the budget impact of funding these medicines (353).

5. Which funding model could be adopted for ATMPs?

There are no perfect models. A likely sustainable model for ATMPs may be an "ATMP specific fund" independent from the traditional existing reimbursement path and independently funded. It is a special fund associated to other funding models to ensure its sustainability. Lessons can be learned from CDF experience in UK to avoid repeating the same errors, and provide rapid sustained access to ATMPs without reaching an unbearable stage (354).

In this model, funds sources would be tax-based. Eligibility criteria should be clearly defined to restrict the entry for highly innovative effective ATMPs with high upfront cost and downstream delayed dramatic outcomes. An "ATMP value assessment framework" may be needed. The ICER threshold may be revised down while the discount rate may be revised up for example to adjust prices of ATMP to affordability (size of the fund). Ultimately, the investment in ATMPs will also need to be contained within a predefined limited budget. Therefore, all cost containment measures could be applied. The various discounts/rebates/price volume agreement/cost sharing/ annuity payment may apply to render those products more affordable but this may certainly not be the cornerstone of funding ATMP.

To avoid the uncertainty on the added value of funded therapies like with CDF which was considered a waste of money by some authors (355, 356), CED with escrow agreement should be the rule as most of those highly promising therapy will reach the market with immature data.. Such scheme would allow maintaining a major pillar of innovation: the value based pricing. A robust and effective horizon scanning will be a critical tool to allow a strong forecasting of requested resources to fund ATMPs or to secure prices of ATMPs are aligned with budget. Finally, the government will need to define a maximal proportion of GDP allocated to this fund.

It is critical to keep in mind that by channeling an excessive budget to health care interventions, resources are displaced from health determinants (e.g. clean fresh water, education, social services, pollution control, etc…) which may contribute to citizen health worsening. This may be a health disinvestment rather than a health investment. The choice of the displaced resource allocation will be as important as the new funded intervention.

Conclusion & Recommendations

1. Conclusion

ATMP is a heterogeneous class of modern cutting-edge biotechnology medicines. ATMPs hold promising potential of curing many chronic and disabling diseases which have high clinical unmet needs.

ATMPs differ from other pharmaceuticals on different levels: manufacturing (short shelf lives, no bulk production possible), safety concerns (immune reactions, tumorgenecity, etc…), clinical evidence generation – small population, no clear comparator and surrogate endpoints – and uncertainties due to limited evidence at time of launch. Several hurdles are facing the ATMPs, this makes a successful market access a critical and difficult step. Indeed, the first 4 of the 9 ATMPs that have been granted a MA in EU, are withdrawn from the European market.

The current pipeline of potential ATMPs includes ATMPs targeting a wide range of diseases previously considered untreatable. Around 735 ATMPs clinical trials are currently ongoing in different phases of development (phase 1, 1/2, 2, 2/3, and 3) targeting a number of conditions such as cancers, cardiovascular diseases, musculoskeletal and neurological diseases, as well as immune system and inflammatory disorders. The large number of ATMPs in development is likely to continue to grow fueled by many products in pilot human development phase. Already 65 studies are phase 3 and 21 studies are combined phase 2/3. This suggests that some of those products will reach the market soon. ATMPs represent a fast growing field of interest.

The high clinical potential is usually associated to a high price. ATMPs are expected to have a substantial impact on health insurance budget and may exceed the annual healthcare expenditure. ATMPs will raise affordability concerns and healthcare system sustainability issue.

We are entering an era in the pharmaceutical industry where cost-effective does not necessarily mean affordable. As we have demonstrated, even if the price of ATMP is determined using a value-based approach, the budget impact will be unbearable by payers. ATMPs may sink the health insurance budget especially on the short term.

The traditional pricing policies may be insufficient to maintain the sustainability of healthcare system. A reshape of the health policies is needed to be ready for the arrival of breakthrough therapies to the market.

2. Recommendations

In conclusion, the current pricing and market access pathways used worldwide may not be adapted to ATMPs. Innovative therapies need innovative policies and market access strategies. Changes need to be adopted on all the three market access dimensions in order to ensure patient access to innovative ATMPs, address the affordability issue and maintain the health system systainability.

1. The first dimension is at stakeholders level.

The five key stakeholders including pharmaceutical companies, regulators, payers, physicians and patients will need to collaborate and discuss to find new approaches or system reforms specific for ATMPs.

Evidence generation practical limits need to be understood by payers and regulators. On the other hand, pharmaceutical companies, physicians and patients need to understand the budget constraints under which the payers are operating nowadays.

There are three types of early dialogues (357):

- To facilitate the feedback collection on the development plan by the manufacturers from the regulators and health technology assessment bodies (HTA)/payers, EMA started the parallel scientific advices in July 2010. It is an early dialogue between pharmaceutical companies, regulators as well as HTA bodies. The parallel scientific advice helps to collect simulatneously feedback on the requirements of regulators and HTa bodies. According to Professor Guido Rasi, EMA's Executive Director said: "*This ensures that patients only participate in well-designed clinical trials that generate the evidence needed for both regulatory and health technology assessment. Ultimately, this will improve timely access by patients to meaningful new medicines across Europe for the benefit of public health" (358)*.
- National early HTA advice is another option. Several countries like France and UK have put in place this procedure. It is an early dialogue between the manufacturer and a national HTA of a country of his choice.
- A multi-national dialogue is also another option; it consists of cooperative advice from EU national HTA bodies. It is sponsored by the European

Commission. It ensures an improvement of the development plans of new technologies and the additional data collection. Multi-HTA avoids the duplication of work and increase transparency.

2. The second dimension is the spatio-temporal dimension (pre, peri and post launch).

To ensure the successful market access of an ATMP, the market access roadmap should be very carefully prepared during the pre-launch and peri-launch phases, starting early stages of development. Generating robust clinical evidence is a challenge before the launch of the ATMP. RCT are the golden standard. However, due to the limited population sizes in some cases or ethical reasons RCT may be not possible, seeking a coverage with evidence development may be a solution to reduce the uncertainty associated with the arrival of the ATMP to the market.

Evidence generation post-launch will become unavoidable to address payers' expectations. Real world evidence needs to be collected through patients registries. this needs a collaboration between physicians, patients and manufacturers.

3. The third dimension is the value-outcomes and pricing dimensions

The biggest challenge is the affordability. ATMPs are accused to be a future threat for the sutainability of the healthcare system. Therefore, manufacturers need to be prepared to justify with robust evidence the high prices claimed for their ATMPs.

At payers level, as a large number of ATMPs is currently in development, it is time for payers to start thinking and embracing new funding strategies for these innovative therapies. traditional payment models need to change to keep pace with medical innovation.

The frequently proposed annuity payment may not be the appropriate way forward. Instead, an "ATMP-specific fund" with clearly defined eligibility criteria may constitute a reasonable and practical solution. Furthermore, using usual cost containment measures may be necessary to adjust prices to affordability, and a CED with escrow agreements will likely be needed to address uncertainty.

These approaches ensures patient access to innovation without threatening the financial sustainability of the health insurance. A collaboration between manufacturers and payers is important to anticipate the arrival of ATMPs to the market. A broader perspective should be considered to ensure that resources are not channeled out of health determinants and that opportunity cost is considered.

Bibliography

1. European Commission. Economic Crisis in Europe: Causes, Consequences and Responses. Directorate-General for Economic and Financial Affairs; 2009.

2. Amadeo K. Eurozone Debt Crisis: Causes, Cures and Consequences2016 23/04/2017.

3. Eurostat. General government gross debt. http://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tsdde410&plugin=12016.

4. Eurostat. Healthcare expenditure statistics 2017 [Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Healthcare_expenditure_statistics.

5. OECD. Pharmaceutical spending [Available from: https://data.oecd.org/healthres/pharmaceutical-spending.htm.

6. Medearis A, Hishow O. Narrowing the sustainability gap of EU and US health care spending. working papers. SWP 2010.

7. Maciulaitis R, D'Apote L, Buchanan A, Pioppo L, Schneider CK. Clinical Development of Advanced Therapy Medicinal Products in Europe: Evidence That Regulators Must Be Proactive. Molecular Therapy. 2012;20(3):479-82.

8. Touchot N, Flume M. Early Insights from Commercialization of Gene Therapies in Europe. Genes. 2017;8(2):78.

9. Silverman E. Cancer drug prices are high at launch and stay that way 2016 [Available from: https://www.statnews.com/pharmalot/2016/05/02/cancer-drug-prices-keep/.

10. Goldstein DA, Stemmer SM, Gordon N. The cost and value of cancer drugs – are new innovations outpacing our ability to pay? Isr J Health Policy Res. 2016;5:40.

11. Durkee BY, Qian Y, Pollom EL, King MT, Dudley SA, Shaffer JL, et al. Cost-Effectiveness of Pertuzumab in Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. J Clin Oncol. 2016;34(9):902-9.

12. Médicaments innovants: les labos accusés de "marges exorbitantes" 2016 [Available from: http://www.linguee.com/english-french/search?source=auto&query=d%C3%A9noncer+le+prix.

13. EMA. Sovaldi [Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002798/human_med_001723.jsp&mid=WC0b01ac058001d124.

14. Kamar N, Marion O, Rostaing L, Cointault O, Ribes D, Lavayssiere L, et al. Efficacy and Safety of Sofosbuvir-Based Antiviral Therapy to Treat Hepatitis C Virus Infection After Kidney Transplantation. Am J Transplant. 2016;16(5):1474-9.

15. Lawitz E, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, et al. Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection. N Engl J Med. 2013;368(20):1878-87.

16. Jacobson IM, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, et al. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. N Engl J Med. 2013;368(20):1867-77.

17. Zeuzem S, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, et al. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. N Engl J Med. 2014;370(21):1993-2001.

18. Barlas S. Are Specialty Drug Prices Destroying Insurers and Hurting Consumers?: A Number of Efforts Are Under Way to Reduce Price Pressure. Pharmacy and Therapeutics. 2014;39(8):563-6.

19. La nouvelle républiquefr [Internet]2014. Available from: http://www.lanouvellerepublique.fr/France-Monde/Actualite/Sante/n/Contenus/Articles/2014/07/10/Le-Sovaldi-ce-medicament-contre-l-hepatite-C-au-prix-faramineux-1979429.

20. Lee D, Hanna E, El Hammi E, Remuzat C, Toumi M. Sofosbuvir: The Failure of Pricing Policies In The European Union. Value Health. 2015;18(7):A572-3.

21. Gregson N, Sparrowhawk K, Mauskopf J, Paul J. Pricing medicines: theory and practice, challenges and opportunities. Nat Rev Drug Discov. 2005;4(2):121-30.

22. Gandhi B. An Overview of the Advances Made in Biotechnology and Related BTWC Concerns. Journal on Chemical and Biological Weapons. 2011.

23. Banerji R, Mukherjee G, Pandey A, Sabu A. Developments in Biotechnology: An overview. Indian Journal of biotechnology. 2002;1(January 2002):9-16.

24. REGULATION (EC) No 1394/2007 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004, (2007).

25. The European Parliament and the Council of the European Union, Directive 2001/83/EC, (2001).

26. EMA. ATMPs Legal framework 2011 [Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000295.jsp&murl=menus/regulations/regulations.jsp&mid=WC0b01ac058007f4bb.

27. The European Parliament and the Council of the European Union, Directive 2004/23/EC (2004).

28. TERMIS PAP: Session 3—Regulation of Advanced Therapeutic Medicinal Products (ATMPs) in Europe [Available from: https://medium.com/termisbpc/termis-pap-session-3-regulation-of-advanced-therapeutic-medicinal-products-atmps-in-europe-fd7f883a9c81.

29. Kaji EH, Leiden JM. Gene and stem cell therapies. Jama. 2001;285(5):545-50.

30. Yee C. Adoptive T-Cell Therapy for Cancer: Boutique Therapy or Treatment Modality? Clin Cancer Res. 2013;19(17):4550-2.

31. Autologous Chondrocyte Implantation (ACI) [Available from: http://www.drgilljointreplacementsurgeon.com/autologous-chondrocyte-implantation-aci/.

32. Pacini S. Deterministic and stochastic approaches in the clinical application of mesenchymal stromal cells (MSCs). Frontiers in Cell and Developmental Biology. 2014;2(50).

33. Van Wilder P. Advanced Therapy Medicinal Products and Exemptions to the Regulation 1394/2007: How Confident Can We be? An Exploratory Analysis. Front Pharmacol. 2012;3:12.

34. European Commission PC. Hospital exemption for ATMPs (implementation of Art 28(2) of Regulation 1394/2007): update on feedback received by the Commission. 2012.

35. Ancans J. Cell therapy medicinal product regulatory framework in Europe and its application for MSC-based therapy development. Frontiers in Immunology. 2012;3:253.

36. European Medicines Agency - Advanced therapy classification - Summaries of scientific recommendations on classification of advanced therapy medicinal products [28/04/2017]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000301.jsp&mid=WC0b01ac05800862c0.

37. Luria X, BR. S. Handbook about Regulatory Guidelines and Procedures for the Preclinical and Clinical Stages of Advanced Therapy Medicinal Products (ATMPs).

38. Kooijman M, van Meer PJ, Gispen-de Wied CC, Moors EH, Hekkert MP, Schellekens H. The risk-based approach to ATMP development - generally accepted by regulators but infrequently used by companies. Regul Toxicol Pharmacol. 2013;67(2):221-5.

39. EMA. Guideline on the risk-based approach according to annex I, part IV of Directive 2001/83/EC applied to Advanced therapy medicinal products. 2013.

40. Guideline on the quality, non-clinical and clinical aspects 4 of gene therapy medicinal products, (2015).

41. Guideline on human cell-based medicinal products, (2008).

42. EMA. Guidelines relevant for advanced therapy medicinal products [Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000298.jsp#celltherapy.

43. EMA. Procedural advice on the evaluation of advanced therapy medicinal product in accordance with Article 8 Of Regulation (EC) NO 1394/2007. 2009.

44. EMA. Explanatory note on general fees payable to the European Medicines Agency 2016 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2016/03/WC500203971.pdf.

45. EMA. European Medicines Agency pre-authorisation procedural advice for users of the centralised procedure 2017 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500004069.pdf.

46. REGULATION (EC) No 726/2004 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL, (2004).

47. EMA. Development support and regulatory tools for early access to medicines. 2016.

48. EMA. Innovation Task Force. 2013.

49. EMA. User guide for micro, small and medium-sized enterprises on the administrative and procedural aspects of the provisions laid down in Regulation (EC) No 726/2004, that are of particular relevance to SMEs. 2016.

50. Guideline on safety and efficacy follow-up - risk management of Advanced Therapy Medicinal Products, (2008).

51. EMA. Risk Management of Advanced Therapies 2009 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2009/11/WC500007629.pdf.

52. EMA. Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products 2008 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2009/10/WC500006326.pdf.

53. European Medicines Agency, Chondrocelect EPAR 2014 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000878/WC500026031.pdf.

54. European Medicines Agency, Glybera EPAR 2015 [28/04/2017]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002145/human_med_001480.jsp&mid=WC0b01ac058001d124.

55. European Medicines Agency, MACI EPAR 2013 [28/04/2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002522/WC500145889.pdf.

56. European Medicines Agency, Provenge EPAR 2013 [28/04/2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002513/WC500151157.pdf.

57. European Medicines Agency, Holoclar EPAR 2015 [28/04/2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002450/WC500183406.pdf.

58. European Medicines Agency, Imlygic EPAR 2015 [28/04/2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002771/WC500201080.pdf.

59. European Medicines Agency, Strimvelis EPAR 2016 [28/04/2017]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/003854/WC500208202.pdf.

60. European Medicines Agency, Zalmoxis EPAR 2016 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/002801/WC500212516.pdf.

61. EMA. EPAR Spherox 2017 [Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002736/human_med_002138.jsp&mid=WC0b01ac058001d124.

62. Abou-El-Enein M, Elsanhoury A, Reinke P. Overcoming Challenges Facing Advanced Therapies in the EU Market. Cell Stem Cell.19(3):293-7.

63. European Commission Consultation Document, Good Manufacturing Practice for Advanced Therapy Medicinal Products. 2016.

64. Smith MD, Brune JC, Wildemann B, Pruss A. Whither Advanced Therapy Medicinal Products? Transfusion Medicine and Hemotherapy. 2013;40(6):449-52.

65. Directive 2004/23/ec of the european parliament and of the council of 31 March 2004 on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells, (2004).

66. Commission directive 2006/17/EC of 8 February 2006 implementing Directive 2004/23/EC of the European Parliament and of the Council as regards certain technical requirements for the donation, procurement and testing of human tissues and cells, (2006).

67. Commission directive 2006/86/ec of 24 october 2006 implementing directive 2004/23/ec of the European parliament and of the council as regards traceability requirements, notification of serious adverse reactions and events and certain technical requirements for the coding, processing, preservation, storage and distribution of human tissues and cells, (2006).

68. EMA. Guideline on scientific requirements for the environmental risk assessment of gene therapy medicinal products 2008.

69. First-in-human clinical studies: challenges for ATMPs. Regulatory Rapporteur [Internet]. 2013.

70. Bryant LM, Christopher DM, Giles AR, Hinderer C, Rodriguez JL, Smith JB, et al. Lessons learned from the clinical development and market authorization of Glybera. Hum Gene Ther Clin Dev. 2013;24(2):55-64.

71. Hettle R. The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal. NIHR (NHS National Institute for Health Research); 2017.

72. Tigenix. TiGenix obtains national reimbursement in the Netherlands for breakthrough cartilage therapy ChondroCelect®. 2012.

73. Tigenix. TiGenix obtains reimbursement for ChondroCelect in Belgium and gives update on reimbursement status in other European countries. 2011.

74. Tigenix. TiGenix to obtain national reimbursement in Spain for its innovative cartilage therapy ChondroCelect®. 2013.

75. HAS. Transparency committee opinion: Chondrocelect. HAS Website: HAS; 2013 29 May 2013

76. NICE. National Institute For Health And Care Excellence Centre For Health Technology Evaluation technology Appraisals, Consultation on Batch 30 and Batch 31 draft remits and draft scopes and summary of comments and discussions at scoping workshops. 2015.

77. Prescott C, Prolak DJ. The delivery of regenreative medicines and their impact on healthcare: CRC Press; 2016.

78. HAS. Transparency Committee Opinion: Glybera 2015 [Available from: http://www.has-sante.fr/portail/upload/docs/application/pdf/2016-05/glybera_summary_ct14224.pdf.

79. G-BA. Zusatznutzen von Glybera® (Wirkstoff: Alipogentiparvovec) nicht quantifizierbar 2015 [28/04/2017]. Available from: https://www.g-ba.de/institution/presse/pressemitteilungen/578/.

80. G-BA. zum Beschluss über eine Änderung der Richtlinie Methoden Krankenhausbehandlung: Autologe Chondrozytenimplantation (ACI) 2014 [28/04/2017]. Available from: https://www.g-ba.de/downloads/40-268-2802/2014-05-22_KHMe-RL_ACI_ZD.pdf.

81. National Institute For Health And Care Excellence: Final appraisal determination Sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer 2015 [28/04/2017]. Available from: https://www.nice.org.uk/guidance/ta332/documents/prostate-cancer-metastatic-hormone-relapsed-sipuleucelt-1st-line-id573-final-appraisal-determination-document2.

82. G-BA. Provenge Beschluss 2015 [28/04/2017]. Available from: https://www.g-ba.de/informationen/nutzenbewertung/143/.

83. HAS. Transparency Committe opinion, Holoclar 2016 [28/04/2017]. Available from: http://www.has-sante.fr/portail/jcms/c_2661389/fr/holoclar-cellules-souches-limbiques-autologues-amplifiees-cellules-souches-pour-transplantation-autologue.

84. NICE. Holoclar for treating limbal stem cell deficiency after eye burns NICE website2017 [Available from: https://www.nice.org.uk/guidance/ta467/chapter/1-Recommendations.

85. Volmer T, Bakker K. The assessment of advanced medicinal products (atmp) in germany: is the practice to define atmp drugs as procedures in compliance with european legislation? Value Health.19(7):A442.

86. NICE. Melanoma (metastatic) - talimogene laherparepvec [ID508] 2016 [Available from: https://www.nice.org.uk/guidance/indevelopment/gid-tag509.

87. IQWIG. Talimogene laherparepvec in melanoma: added benefit not proven 2016 [28/04/2017]. Available from: https://www.iqwig.de/en/press/press-releases/press-releases/talimogene-laherparepvec-in-melanoma-added-benefit-not-proven.7563.html.

88. Closure of EU manufacturing site 2014 [28/04/2017]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Maci/human_referral_000380.jsp&mid=WC0b01ac05805c516f.

89. Jaroslawski S, Toumi M. Sipuleucel-T (Provenge((R)))-Autopsy of an Innovative Paradigm Change in Cancer Treatment: Why a Single-Product Biotech Company Failed to Capitalize on its Breakthrough Invention. BioDrugs. 2015;29(5):301-7.

90. EMA. Provenge: Withdrawal of the marketing authorisation in the European Union 2015 [Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Public_statement/2015/05/WC500186950.pdf.

91. Tigenix. TiGenix reconfirms its strategic focus on its allogeneic stem cell platforms. 2016.

92. uniQure announces it will not seek marketing authorization renewal for Glybera in Europe [Internet]. 2017. Available from: www.uniQure.com.

93. Valeant. Valeant Pharmaceuticals Completes Sale Of Dendreon To Sanpower Group 2017 [Available from: http://ir.valeant.com/news-releases/2017/06-29-2017-120234317.

94. Gnecchi M, Zhang Z, Ni A, Dzau VJ. Paracrine mechanisms in adult stem cell signaling and therapy. Circ Res. 2008;103(11):1204-19.

95. Bron JL, Helder MN, Meisel H-J, Van Royen BJ, Smit TH. Repair, regenerative and supportive therapies of the annulus fibrosus: achievements and challenges. European Spine Journal. 2009;18(3):301-13.

96. Galli MC. ATMPs for Cancer Immunotherapy: A Regulatory Overview. In: Bondanza A, Casucci M, editors. Tumor Immunology: Methods and Protocols. New York, NY: Springer New York; 2016. p. 1-9.

97. Kumar SRP, Markusic DM, Biswas M, High KA, Herzog RW. Clinical development of gene therapy: results and lessons from recent successes. Molecular Therapy Methods & Clinical Development. 2016;3:16034.

98. Boye SE, Boye SL, Lewin AS, Hauswirth WW. A comprehensive review of retinal gene therapy. Molecular therapy : the journal of the American Society of Gene Therapy. 2013;21(3):509-19.

99. Testa F, Maguire AM, Rossi S, Pierce EA, Melillo P, Marshall K, et al. Three-year follow-up after unilateral subretinal delivery of adeno-associated virus in patients with Leber congenital Amaurosis type 2. Ophthalmology. 2013;120(6):1283-91.

100. Aiuti A, Cattaneo F, Galimberti S, Benninghoff U, Cassani B, Callegaro L, et al. Gene therapy for immunodeficiency due to adenosine deaminase deficiency. N Engl J Med. 2009;360(5):447-58.

101. Mertsching H, Walles T. Europe's Advanced Therapy Medicinal Products: chances and challenges. Expert Review of Medical Devices. 2009;6(2):109-10.

102. Trounson A, McDonald C. Stem Cell Therapies in Clinical Trials: Progress and Challenges. Cell Stem Cell.17(1):11-22.

103. Bisson I, Green E, Sharpe M, Herbert C, Hyllner J, Mount N. Landscape of current and emerging cell therapy clinical trials in the UK: current status, comparison to global trends and future perspectives. Regen Med. 2015;10(2):169-79.

104. Ginn SL, Alexander IE, Edelstein ML, Abedi MR, Wixon J. Gene therapy clinical trials worldwide to 2012 - an update. The journal of gene medicine. 2013;15(2):65-77.

105. (WHO) WHO. Health Promotion Evaluation: Recommendations to Policymakers. 1998.

106. Svennebring AM, Wikberg JE. Net present value approaches for drug discovery. Springerplus. 2013;2(1):140.

107. Kasenda B, von Elm E, You J, Blumle A, Tomonaga Y, Saccilotto R, et al. Prevalence, characteristics, and publication of discontinued randomized trials. Jama. 2014;311(10):1045-51.

108. Sanzenbacher R, Dwenger A, Schuessler-Lenz M, Cichutek K, Flory E. European regulation tackles tissue engineering. Nat biotechnol. 2007;25(10):1089-91.

109. Commission directive 2009/120/EC of 14 September 2009 amending Directive 2001/83/EC of the European Parliament and of the Council on the Community code relating to medicinal products for human use as regards advanced therapy medicinal products, (2009).

110. Clinicaltrials.gov: Glossary of common site terms [Available from: https://clinicaltrials.gov/ct2/about-studies/glossary.

111. Rosenberg SA, Aebersold P, Cornetta K, Kasid A, Morgan RA, Moen R, et al. Gene transfer into humans--immunotherapy of patients with advanced melanoma, using tumor-infiltrating lymphocytes modified by retroviral gene transduction. N Engl J Med. 1990;323(9):570-8.

112. French gene therapy group reports on the adverse event in a clinical trial of gene therapy for X-linked severe combined immune deficiency (X-SCID). The journal of gene medicine. 2003;5(1):82-4.

113. Gansbacher B. Report of a second serious adverse event in a clinical trial of gene therapy for X-linked severe combined immune deficiency (X-SCID). The journal of gene medicine. 2003;5(3):261-2.

114. Marshall E. Gene therapy death prompts review of adenovirus vector. Science. 1999;286(5448):2244-5.

115. Raper SE, Chirmule N, Lee FS, Wivel NA, Bagg A, Gao GP, et al. Fatal systemic inflammatory response syndrome in a ornithine transcarbamylase deficient patient following adenoviral gene transfer. Mol Genet Metab. 2003;80(1-2):148-58.

116. Hacein-Bey-Abina S, Garrigue A, Wang GP, Soulier J, Lim A, Morillon E, et al. Insertional oncogenesis in 4 patients after retrovirus-mediated gene therapy of SCID-X1. The Journal of clinical investigation. 2008;118(9):3132-42.

117. Yla-Herttuala S. Endgame: glybera finally recommended for approval as the first gene therapy drug in the European union. Molecular therapy : the journal of the American Society of Gene Therapy. 2012;20(10):1831-2.

118. EMA. Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of regulation (ec) no 726/2004. 2005.

119. Wilkinson B , Bennett C. Will reimbursement prove to be the biggest barrier as three gene therapies gain regulatory approval? . 2016.

120. Celis P, Ferry N, Hystad M, Schüßler-Lenz M, Doevendans PA, Flory E, et al. Advanced Therapy Medicinal Products: How to Bring Cell-Based Medicinal Products Successfully to the Market – Report from the CAT-DGTI-GSCN Workshop at the DGTI Annual Meeting 2014. Transfusion Medicine and Hemotherapy. 2015;42(3):194-9.

121. Keyhani S, Wang S, Hebert P, Carpenter D, Anderson G. US Pharmaceutical Innovation in an International Context. Am J Public Health. 2010;100(6):1075-80.

122. Cockburn IM. The changing structure of the pharmaceutical industry. Health Aff (Millwood). 2004;23(1):10-22.

123. McGovern V. Getting grants. Virulence. 2012;3(1):1-11.

124. Non-NIH grants [29/04/2017]. Available from: http://socialwork.nyu.edu/faculty-and-staff/office-for-research/grants-pre-award/non-nih-grants.html.

125. Wright M. Academic entrepreunership in Europe: Edward Elgar Publishing; 2007.

126. OECD. Tax incentives for research and development: Trends and issues

127. Corporation Tax: Research and Development tax relief 2016 [29/04/2017]. Available from: https://www.gov.uk/guidance/corporation-tax-research-and-development-rd-relief.

128. Nayerossadat N, Maedeh T, Ali PA. Viral and nonviral delivery systems for gene delivery. Advanced Biomedical Research. 2012;1:27.

129. Hirai H, Satoh E, Osawa M, Inaba T, Shimazaki C, Kinoshita S, et al. Use of EBV-based Vector/HVJ-liposome complex vector for targeted gene therapy of EBV-associated neoplasms. Biochem Biophys Res Commun. 1997;241(1):112-8.

130. Nayak S, Herzog RW. Progress and prospects: immune responses to viral vectors. Gene therapy. 2010;17(3):295-304.

131. Bowles DE, McPhee SW, Li C, Gray SJ, Samulski JJ, Camp AS, et al. Phase 1 gene therapy for Duchenne muscular dystrophy using a translational optimized AAV vector. Molecular therapy : the journal of the American Society of Gene Therapy. 2012;20(2):443-55.

132. PhRMA. Nearly 800 New Medicines in Development to Fight Cancer 2014 [28/04/2017]. Available from: http://www.phrma.org/press-release/nearly-800-new-medicines-in-development-to-help-in-the-fight-against-cancer.

133. Buffery D. The 2015 Oncology Drug Pipeline: Innovation Drives the Race to Cure Cancer. Am. 2015;8(4):216-22.

134. Boudes PF. Gene therapy as a new treatment option for inherited monogenic diseases. Eur J Intern Med. 2014;25(1):31-6.

135. Picavet E, Dooms M, Cassiman D, Simoens S. Drugs for rare diseases: influence of orphan designation status on price. Appl Health Econ Health Policy. 2011;9(4):275-9.

136. Regulation (EC) No 141/2000 of the European parliament and of the council of 16 December 1999 on orphan medicinal products, (2000).

137. Authorisation for State aid pursuant to Articles 87 and 88 of the EC Treaty Cases where the Commission raises no objections, (2002).

138. Eurostat. Causes of death statistics 2016 [29/04/2017]. Available from: http://ec.europa.eu/eurostat/statistics-explained/index.php/Causes_of_death_statistics.

139. WHO. The top 10 causes of death 2017 [29/04/2017]. Available from: http://www.who.int/mediacentre/factsheets/fs310/en/.

140. Townsend N, Nichols M, Scarborough P, Rayner M. Cardiovascular disease in Europe — epidemiological update 2015. Eur Heart J. 2015;36(40):2696-705.

141. WHO. Data and statistics [29/04/2017]. Available from: http://www.euro.who.int/en/health-topics/noncommunicable-diseases/cancer/data-and-statistics.

142. EC. The 2014 EU summit on chronic diseases Brussels, 3 and 4 April 2014, conference conclusions. 2014.

143. WHO. The global burden of chronic [29/04/2017]. Available from: http://www.who.int/nutrition/topics/2_background/en/.

144. Kaitin KI, DiMasi JA. Pharmaceutical innovation in the 21st century: new drug approvals in the first decade, 2000-2009. Clin Pharmacol Ther. 2011;89(2):183-8.

145. Mullard A. New drugs cost US[dollar]2.6 billion to develop. Nat Rev Drug Discov. 2014;13(12):877-.

146. Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Transforming Clinical Research in the United States: Challenges and Opportunities: Workshop Summary. Washington (DC): National Academies Press (US)2010.

147. Lièvre M, Ménard J, Bruckert E, Cogneau J, Delahaye F, Giral P, et al. Premature discontinuation of clinical trial for reasons not related to efficacy, safety, or feasibility. BMJ : British Medical Journal. 2001;322(7286):603-6.

148. Stensland K, Latif A, Hendricks R, Roper N, McBride R, Hall S, et al. Prevalence and characteristics of prematurely terminated cancer clinical trials. 2013 ASCO Annual Meeting; 2013 May 31. 2013 Jun 04; Chicago, IL2013.

149. Bernardez-Pereira S, Lopes RD, Carrion MJ, Santucci EV, Soares RM, de Oliveira Abreu M, et al. Prevalence, characteristics, and predictors of early termination of cardiovascular clinical trials due to low recruitment: insights from the ClinicalTrials.gov registry. Am Heart J. 2014;168(2):213-9.e1.

150. Kantarjian H, Steensma D, Sanjuan JR, Elshaug A, Light D. High Cancer Drug Prices in the United States: Reasons and Proposed Solutions. Journal of Oncology Practice. 2014;10(4):e208-e11.

151. Pfister DG. The Just Price of Cancer Drugs and the Growing Cost of Cancer Care: Oncologists Need to Be Part of the Solution. J Clin Oncol. 2013;31(28):3487-9.

152. Chouaid C, Borget I, Braun E, Bazil ML, Schaetz D, Remuzat C, et al. French Health Technology Assessment of Antineoplastic Drugs Indicated in the Treatment of Solid Tumours: Perspective for Future Trends. Target Oncol. 2016;11(4):515-34.

153. EMA. European Medicines Agency recommends 39 medicines for human use for marketing authorisation in first half of 2014 2014 [29/04/2017]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2014/07/news_detail_002135.jsp&mid=WC0b01ac058004d5c1.

154. Cylus J, Mladovsky P, McKee M. Is there a statistical relationship between economic crises and changes in government health expenditure growth? an analysis of twenty-four European countries. Health Serv Res. 2012;47(6):2204-24.

155. Drummond MF, Wilson DA, Kanavos P, Ubel P, Rovira J. Assessing the economic challenges posed by orphan drugs. Int J Technol Assess Health Care. 2007;23(1):36-42.

156. Morrison C. $1-million price tag set for Glybera gene therapy. Nat biotechnol. 2015;33(3):217-8.

157. Siddiqui M, Rajkumar SV. The High Cost of Cancer Drugs and What We Can Do About It. Mayo Clin Proc. 2012;87(10):935-43.

158. Luengo-Fernandez R, Leal J, Gray A, Sullivan R. Economic burden of cancer across the European Union: a population-based cost analysis. Lancet Oncol. 2013;14(12):1165-74.

159. ESMO. The first ever estimate of the economic burden of cancer in Europe shows that it exceeds 124 billion euros. 2012.

160. WHO. Access to new medicines in Europe: technical review of policy initiatives and opportunities for collaboration and research. 2015.

161. Anastasaki E, Bradshaw S, Walker A. An update on market access for Advanced-Therapy Medicinal Products In Europe. International Health Economics and Outcomes Research (ISPOR) 17TH Annual European Congress,; 8–12 November 2014; Amsterdam, The Netherlands2014.

162. Hanna E, Remuzat C, Auquier P, Toumi M. Advanced therapy medicinal products: current and future perspectives. Journal of market access & health policy. 2016;4.

163. Jørgensen J, Kefalas P. Reimbursement of licensed cell and gene therapies across the major European healthcare markets. Journal of market access & health policy. 2015;3:10.3402/jmahp.v3.29321.

164. Toumi M, Rémuzat C, El Hammi E, Millier A, Aballéa S, Chouaid C, et al. Current process and future path for health economic assessment of pharmaceuticals in France. Journal of market access & health policy. 2015;3:10.3402/jmahp.v3.27902.

165. Italian Medicines Agency (AIFA) Lista aggiornata dei Registri. [Available from: http://www.agenziafarmaco.gov.it/it/content/lista-aggiornata-dei-registri.

166. McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: what it is and what that means. Pharmacoeconomics. 2008;26(9):733-44.

167. NICE. NICE gets go-ahead to fast-track more drug approvals 2017 [Available from: https://www.nice.org.uk/news/article/nice-gets-go-ahead-to-fast-track-more-drug-approvals.

168. Mauskopf JA, Sullivan SD, Annemans L, Caro J, Mullins CD, Nuijten M, et al. Principles of Good Practice for Budget Impact Analysis: Report of the ISPOR Task Force on Good Research Practices—Budget Impact Analysis. Value Health. 2007;10(5):336-47.

169. van de Vooren K, Duranti S, Curto A, Garattini L. A critical systematic review of budget impact analyses on drugs in the EU countries. Appl Health Econ Health Policy. 2014;12(1):33-40.

170. Jankovic J. Parkinson's disease: clinical features and diagnosis. J Neurol Neurosurg Psychiatry. 2008;79(4):368-76.

171. Gustavsson A, Svensson M, Jacobi F, Allgulander C, Alonso J, Beghi E, et al. Cost of disorders of the brain in Europe 2010. European neuropsychopharmacology : the journal of the European College of Neuropsychopharmacology. 2011;21(10):718-79.

172. Thanvi B, Lo T. Long term motor complications of levodopa: clinical features, mechanisms, and management strategies. Postgraduate Medical Journal. 2004;80(946):452-8.

173. Lindvall O, Widner H, Rehncrona S, Brundin P, Odin P, Gustavii B, et al. Transplantation of fetal dopamine neurons in Parkinson's disease: one-year clinical and neurophysiological observations in two patients with putaminal implants. Ann Neurol. 1992;31(2):155-65.

174. Caiazzo M, Dell'Anno MT, Dvoretskova E, Lazarevic D, Taverna S, Leo D, et al. Direct generation of functional dopaminergic neurons from mouse and human fibroblasts. Nature. 2011;476(7359):224-7.

175. Clinicaltrials.gov [Available from: https://clinicaltrials.gov/ct2/results?term=stem+cells+AND+parkinson%27s.

176. Moore C. Are Parkinson's Disease Stem-cell Therapies Finally Ready for Clinical Trials? It Depends, Some Say 2016 [01/05/2017]. Available from:

https://parkinsonsnewstoday.com/2016/03/31/parkinsons-disease-stem-cell-therapies-finally-ready-clinical-trials-depends-say/.

177. World Alzheimer Report 2015: The Global Impact of Dementia: An analysis of prevalence, incidence, cost and trends. 2015.

178. Black BS, Johnston D, Rabins PV, Morrison A, Lyketsos C, Samus QM. Unmet needs of community-residing persons with dementia and their informal caregivers: findings from the maximizing independence at home study. J Am Geriatr Soc. 2013;61(12):2087-95.

179. Wray S, Fox NC. Stem cell therapy for Alzheimer's disease: hope or hype? The Lancet Neurology.15(2):133-5.

180. Duncan T, Valenzuela M. Alzheimer's disease, dementia, and stem cell therapy. Stem Cell Research & Therapy. 2017;8(1):111.

181. Gaucher disease [Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=355.

182. Ambrosy AP, Fonarow GC, Butler J, Chioncel O, Greene SJ, Vaduganathan M, et al. The global health and economic burden of hospitalizations for heart failure: lessons learned from hospitalized heart failure registries. J Am Coll Cardiol. 2014;63(12):1123-33.

183. Mosterd A, Cost B, Hoes AW, de Bruijne MC, Deckers JW, Hofman A, et al. The prognosis of heart failure in the general population: The Rotterdam Study. Eur Heart J. 2001;22(15):1318-27.

184. Fauci A, Braunwald E, Kasper D. Harrison's Principles of Internal Medicine. 17th Edition HsPoIM, editor: New York: McGraw-Hill; 2008.

185. Desai AS, McMurray JJ, Packer M, Swedberg K, Rouleau JL, Chen F, et al. Effect of the angiotensin-receptor-neprilysin inhibitor LCZ696 compared with enalapril on mode of death in heart failure patients. Eur Heart J. 2015;36(30):1990-7.

186. Gerber Y, Weston SA, Redfield MM, Chamberlain AM, Manemann SM, Jiang R, et al. A contemporary appraisal of the heart failure epidemic in Olmsted County, Minnesota, 2000 to 2010. JAMA Intern Med. 2015;175(6):996-1004.

187. Zarrinkoub R, Wettermark B, Wandell P, Mejhert M, Szulkin R, Ljunggren G, et al. The epidemiology of heart failure, based on data for 2.1 million inhabitants in Sweden. European journal of heart failure. 2013;15(9):995-1002.

188. Fisher SA, Zhang H, Doree C, Mathur A, Martin-Rendon E. Stem cell treatment for acute myocardial infarction. Cochrane Database Syst Rev. 2015(9).

189. Piepoli MF, Vallisa D, Arbasi M, Cavanna L, Cerri L, Mori M, et al. Bone marrow cell transplantation improves cardiac, autonomic, and functional indexes in acute anterior myocardial infarction patients (Cardiac Study). European journal of heart failure. 2010;12(2):172-80.

190. Clifford DM, Fisher SA, Brunskill SJ, Doree C, Mathur A, Clarke MJ, et al. Long-Term Effects of Autologous Bone Marrow Stem Cell Treatment in Acute Myocardial Infarction: Factors That May Influence Outcomes. PLoS ONE. 2012;7(5):e37373.

191. Sanganalmath SK, Bolli R. Cell therapy for heart failure: a comprehensive overview of experimental and clinical studies, current challenges, and future directions. Circ Res. 2013;113(6):810-34.

192. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, Ikram S, et al. Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet. 2011;378(9806):1847-57.

193. Makkar RR, Smith RR, Cheng K, Malliaras K, Thomson LE, Berman D, et al. Intracoronary cardiosphere-derived cells for heart regeneration after myocardial infarction (CADUCEUS): a prospective, randomised phase 1 trial. Lancet. 2012;379(9819):895-904.

194. Jeevanantham V, Butler M, Saad A, Abdel-Latif A, Zuba-Surma EK, Dawn B. Adult bone marrow cell therapy improves survival and induces long-term improvement in cardiac parameters: a systematic review and meta-analysis. Circulation. 2012;126(5):551-68.

195. Patel AN, Henry TD, Quyyumi AA, Schaer GL, Anderson RD, Toma C, et al. Ixmyelocel-T for patients with ischaemic heart failure: a prospective randomised double-blind trial. Lancet. 2016;387(10036):2412-21.

196. Findley LJ, Lees A, Apajasalo M, Pitkanen A, Turunen H. Cost-effectiveness of levodopa/carbidopa/entacapone (Stalevo) compared to standard care in UK Parkinson's disease patients with wearing-off. Curr Med Res Opin. 2005;21(7):1005-14.

197. Zhao YJ, Wee HL, Chan YH, Seah SH, Au WL, Lau PN, et al. Progression of Parkinson's disease as evaluated by Hoehn and Yahr stage transition times. Movement disorders : official journal of the Movement Disorder Society. 2010;25(6):710-6.

198. NICE. Parkinson's disease in over 20s: diagnosis and management 2006 [02/05/2017]. Available from: https://www.nice.org.uk/guidance/cg35/evidence.

199. Hjelmgren J, Ghatnekar O, Reimer J, Grabowski M, Lindvall O, Persson U, et al. Estimating the value of novel interventions for Parkinson's disease: an early decision-making model with application to dopamine cell replacement. Parkinsonism & related disorders. 2006;12(7):443-52.

200. NICE. Parkinson's disease in adults: NICE guideline [NG71] 2017 [Available from: https://www.nice.org.uk/guidance/ng71/chapter/Recommendations#pharmacological-management-of-motor-symptoms.

201. Rinne UK, Larsen JP, Siden A, Worm-Petersen J. Entacapone enhances the response to levodopa in parkinsonian patients with motor fluctuations. Nomecomt Study Group. Neurology. 1998;51(5):1309-14.

202. Durif F, Devaux I, Pere JJ, Delumeau JC, Bourdeix I. Efficacy and tolerability of entacapone as adjunctive therapy to levodopa in patients with Parkinson's disease and end-of-dose deterioration in daily medical practice: an open, multicenter study. Eur Neurol. 2001;45(2):111-8.

203. NICE. Guide to the methods of technology appraisal 2013 2013 [03/05/2017]. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword.

204. Sullivan SD, Mauskopf JA, Augustovski F, Jaime Caro J, Lee KM, Minchin M, et al. Budget impact analysis-principles of good practice: report of the ISPOR 2012 Budget Impact Analysis Good Practice II Task Force. Value Health. 2014;17(1):5-14.

205. NICE. PARKINSON'S DISEASE: National clinical guideline for diagnosis and management in primary and secondary care. In: Conditions TNCCfC, editor. 2006.

206. Evans JR, Cummins G, Breen DP, Foltynie T, Mason SL, Brayne CEG, et al. Comparative epidemiology of incident Parkinson's disease in Cambridgeshire, UK. Journal of Neurology, Neurosurgery & Psychiatry. 2016.

207. Green C, Shearer J, Ritchie CW, Zajicek JP. Model-based economic evaluation in Alzheimer's disease: a review of the methods available to model Alzheimer's disease progression. Value Health. 2011;14(5):621-30.

208. NICE. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease: Technology appraisal guidance [TA217] 2011 [Available from: https://www.nice.org.uk/guidance/TA217.

209. Wimo A, Reed CC, Dodel R, Belger M, Jones RW, Happich M, et al. The GERAS Study: a prospective observational study of costs and resource use in community dwellers with Alzheimer's disease in three European countries--study design and baseline findings. Journal of Alzheimer's disease : JAD. 2013;36(2):385-99.

210. NICE. Donepezil, galantamine, rivastigmine (review) and memantine for the treatment of Alzheimer's disease. National Institute For Health And Clinical Excellence; 2006 May 2006.

211. Bloudek LM, Spackman DE, Veenstra DL, Sullivan SD. CDR state transition probabilities in Alzheimer's disease with and without cholinesterase inhibitor intervention in an observational cohort. Journal of Alzheimer's disease : JAD. 2011;24(3):599-607.

212. Dementia UK update. alzheimers.org.uk/dementiauk; 2014.

213. Matthews FE, Arthur A, Barnes LE, Bond J, Jagger C, Robinson L, et al. A two-decade comparison of prevalence of dementia in individuals aged 65 years and older from three geographical areas of England: results of the Cognitive Function and Ageing Study I and II. Lancet. 2013;382(9902):1405-12.

214. Ford E, Adams J, Graves N. Development of an economic model to assess the cost-effectiveness of hawthorn extract as an adjunct treatment for heart failure in Australia. BMJ Open. 2012;2(5).

215. HAS. Guide du parcours de soins: Insuffisance cardiaque. 2014.

216. Flather MD, Shibata MC, Coats AJ, Van Veldhuisen DJ, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26(3):215-25.

217. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29-322.

218. Yao G, Freemantle N, Flather M, Tharmanathan P, Coats A, Poole-Wilson PA. Long-term cost-effectiveness analysis of nebivolol compared with standard care in elderly patients with heart failure: an individual patient-based simulation model. Pharmacoeconomics. 2008;26(10):879-89.

219. Kelly DJ, Gershlick T, Witzenbichler B, Guagliumi G, Fahy M, Dangas G, et al. Incidence and predictors of heart failure following percutaneous coronary intervention in ST-segment elevation myocardial infarction: the HORIZONS-AMI trial. Am Heart J. 2011;162(4):663-70.

220. Providência R, Boveda S, Defaye P, Segal O, Algalarrondo V, Sadoul N, et al. Outcome of Primary Prevention Implantable Cardioverter Defibrillator Therapy According to New York Heart Association Functional Classification. The American Journal of Cardiology. 2016;118(8):1225-32.

221. Muntwyler J, Abetel G, Gruner C, Follath F. One-year mortality among unselected outpatients with heart failure. Eur Heart J. 2002;23(23):1861-6.

222. Berry C, Murdoch DR, McMurray JJ. Economics of chronic heart failure. European journal of heart failure. 2001;3.

223. OECD. Inflation (IPC) [Available from: https://data.oecd.org/fr/price/inflation-ipc.htm.

224. Calvert MJ, Freemantle N, Yao G, Cleland JG, Billingham L, Daubert JC, et al. Cost-effectiveness of cardiac resynchronization therapy: results from the CARE-HF trial. Eur Heart J. 2005;26(24):2681-8.

225. HAS: Choix méthodologiques pour l'évaluation économique à la HAS

October 2011 [Available from: http://www.has-sante.fr/portail/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=c_2730300.

226. Vemer P, Rutten-van Mölken MPMH. Largely ignored: the impact of the threshold value for a QALY on the importance of a transferability factor. The European Journal of Health Economics. 2011;12(5):397-404.

227. De Peretti C, Pérel C, Tuppin P, Iliou M, Juillière Y, Gabet A. Prévalences et statut fonctionnel des cardiopathies ischémiques et de l'insuffisance cardiaque dans la population adulte en France : apports des enquêtes déclaratives « Handicap-Santé ». Bull Epidémiol Hebd. 2014;(9-10):172-81.

228. Swiss Health Observatory: Heart Failure Incidence 2017 [Available from: http://www.obsan.admin.ch/fr/indicateurs/insuffisance-cardiaque.

229. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol. 2014;171(3):368-76.

230. Maresova P, Klimova B, Novotny M, Kuca K. Alzheimer's and Parkinson's Diseases: Expected Economic Impact on Europe-A Call for a Uniform European Strategy. Journal of Alzheimer's disease : JAD. 2016;54(3):1123-33.

231. Grady D. F.D.A. Approves First Gene-Altering Leukemia Treatment, Costing $475,000 2017 [Available from: https://www.nytimes.com/2017/08/30/health/gene-therapy-cancer.html?mcubz=3.

232. Reeder CE, Gordon D. Managing oncology costs. Am J Manag Care. 2006;12(1 Suppl):S3-16; quiz S7-9.

233. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. Jama. 1996;276(14):1172-7.

234. Findley LJ. The economic impact of Parkinson's disease. Parkinsonism & related disorders. 2007;13 Suppl:S8-s12.

235. McCrone P, Allcock LM, Burn DJ. Predicting the cost of Parkinson's disease. Movement disorders : official journal of the Movement Disorder Society. 2007;22(6):804-12.

236. Tuppin P, Riviere S, Rigault A, Tala S, Drouin J, Pestel L, et al. Prevalence and economic burden of cardiovascular diseases in France in 2013 according to the national health insurance scheme database. Arch Cardiovasc Dis. 2016;109(6-7):399-411.

237. OECD. Health spending [Available from: https://data.oecd.org/healthres/health-spending.htm#indicator-chart.

238. Saraux A. Livre blanc: Chapitre 3: Environnement socio-économique et rhumatologie 2006 [Available from: http://www.rhumatologie.asso.fr/05-Bibliotheque/Livre-Blanc/C6-epidemiologie.asp.

239. HAS. Prise en charge de l'artériopathie chronique oblitérante athéroscléreuse des membres inférieurs - Indications médicamenteuses, de revascularisation et de rééducation 2006 [Available from: https://www.has-sante.fr/portail/jcms/c_272513/fr/prise-en-charge-de-l-arteriopathie-chronique-obliterante-atherosclereuse-des-membres-inferieurs-indications-medicamenteuses-de-revascularisation-et-de-reeducation.

240. HAS. Bronchopneumopathie chronique obstructive 2016 [Available from: https://www.has-sante.fr/portail/jcms/c_1518063/fr/bronchopneumopathie-chronique-obstructive.

241. de Marco R, Accordini S, Cerveri I, Corsico A, Anto JM, Kunzli N, et al. Incidence of chronic obstructive pulmonary disease in a cohort of young adults according to the presence of chronic cough and phlegm. Am J Respir Crit Care Med. 2007;175(1):32-9.

242. INVS. Surveillance épidémiologique de l'asthme en France [Available from: http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Asthme/Surveillance-epidemiologique-de-l-asthme-en-France.

243. solidarité Mdleedl. Prévention et prise en charge de l'asthme 2002 - 2005.

244. INVS. Prévalence et incidence du diabète [Available from: http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Diabete/Donnees-epidemiologiques/Prevalence-et-incidence-du-diabete.

245. Doisy N. 400 nouveaux cas de diabète chaque jour 2017 [Available from: http://www.iau-idf.fr/savoir-faire/environnement/defis-alimentaires/400-nouveaux-cas-de-diabete-chaque-jour.html.

246. HAS. Maladie rénale chronique de l'adulte - Parcours de soins [Available from: https://www.has-sante.fr/portail/jcms/r_1506285/fr/maladie-renale-chronique-de-l-adulte-parcours-de-soins.

247. Stengel B, Combe C, Jacquelinet C, Briancon S, Fouque D, Laville M, et al. The French Chronic Kidney Disease-Renal Epidemiology and Information Network (CKD-REIN) cohort study. Nephrol Dial Transplant. 2014;29(8):1500-7.

248. INVS. Les cardiopathies ischémiques [Available from: http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Maladies-cardio-neuro-vasculaires/Les-cardiopathies-ischemiques.

249. Feigin VL, Forouzanfar MH, Krishnamurthi R, Mensah GA, Connor M, Bennett DA, et al. Global and regional burden of stroke during 1990-2010: findings from the Global Burden of Disease Study 2010. Lancet. 2014;383(9913):245-54.

250. INVS. Les maladies cérébro-vasculaires [Available from: http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Maladies-cardio-neuro-vasculaires/Les-maladies-cerebro-vasculaires.

251. INVS. La maladie d'Alzheimer et les autres démences [Available from: http://invs.santepubliquefrance.fr/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Maladies-neurodegeneratives/La-maladie-d-Alzheimer-et-les-autres-demences.

252. Définition et chiffres de la maladie d'Alzheimer 2015 [Available from: http://alzheimer-recherche.org/la-maladie-alzheimer/quest-maladie-dalzheimer/definition-et-chiffres/.

253. INSERM. Cirrhose [Available from: https://www.inserm.fr/thematiques/physiopathologie-metabolisme-nutrition/dossiers-d-information/cirrhose.

254. HAS. Critères diagnostiques et bilan initial de la cirrhose non compliquée [Available from: https://www.has-sante.fr/portail/plugins/ModuleXitiKLEE/types/FileDocument/doXiti.jsp?id=c_476559.

255. Institut national du cancer: les cancers en France en 2016 l'essentiel des faits et chiffres 2017.

256. HAS. Polyarthrite rhumatoïde : aspects thérapeutiques hors médicaments et chirurgie - aspects médico-sociaux et organisationnels 2007 [Available from: https://www.has-sante.fr/portail/jcms/c_533480/fr/polyarthrite-rhumatoide-aspects-therapeutiques-hors-medicaments-et-chirurgie-aspects-medico-sociaux-et-organisationnels.

257. INVS. La maladie de Parkinson [Available from: http://invs.santepubliquefrance.fr/fr../layout/set/print/Dossiers-thematiques/Maladies-chroniques-et-traumatismes/Maladies-neurodegeneratives/La-maladie-de-Parkinson.

258. Morel. A. La maladie de Crohn, epid emiologie, traitements actuels et en developpement dont l'anticorps anti-int egrine alpha4beta7. HAL 2014.

259. Commission E. Rare diseases in numbers.

260. Matsuo K, Akahoshi M, Nakashima E, Suyama A, Seto S, Hayano M, et al. The prevalence, incidence and prognostic value of the Brugada-type electrocardiogram: a population-based study of four decades. J Am Coll Cardiol. 2001;38(3):765-70.

261. Balwani M, Bloomer J, R D. Porphyrias Consortium of the NIH-Sponsored Rare Diseases Clinical Research Network. Erythropoietic Protoporphyria, Autosomal Recessive. In: GeneReviews®, editor.2012.

262. Syndrome de Guillain-Barré [Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=FR&Expert=2103.

263. Barnes J, Mayes MD. Epidemiology of systemic sclerosis: incidence, prevalence, survival, risk factors, malignancy, and environmental triggers. Curr Opin Rheumatol. 2012;24(2):165-70.

264. Non-Hodgkin lymphoma [Available from: http://eco.iarc.fr/EUCAN/Cancer.aspx?Cancer=38.

265. Multiple myeloma and immunoproliferative diseases [Available from: http://eco.iarc.fr/eucan/cancer.aspx?Cancer=39.

266. Coffin-Lowry syndrome 2010 [Available from: http://www.socialstyrelsen.se/rarediseases/coffin-lowrysyndrome.

267. Polycythemia vera [Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=729.

268. Osler-Weber-Rendu Disease (Hereditary Hemorrhagic Telangiectasia) [Available from: http://emedicine.medscape.com/article/2048472-overview#a6.

269. Microdeletion 22q11 [Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=FR&Expert=567.

270. Kaplan P, Fitzgerald K, C C. Ehlers-Danlos syndrome [Available from: http://www.clinicaladvisor.com/dermatology/ehlers-danlos-syndrome/article/594787/.

271. Syndrome de Stickler [Available from: http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=FR&Expert=828.

272. Cancer of the brain [Available from: http://eco.iarc.fr/EUCAN/Cancer.aspx?Cancer=34.

273. Scotet V, Duguépéroux I, Saliou P, Rault G, Roussey M, Audrézet M-P, et al. Evidence for decline in the incidence of cystic fibrosis: a 35-year observational study in Brittany, France. Orphanet J Rare Dis. 2012;7:14-.

274. Hodgkin lymphoma [Available from: http://eco.iarc.fr/EUCAN/Cancer.aspx?Cancer=37.

275. Bienvenu T, Philippe C, De Roux N, Raynaud M, Bonnefond JP, Pasquier L, et al. The incidence of Rett syndrome in France. Pediatr Neurol. 2006;34(5):372-5.

276. T-B+ severe combined immunodeficiency due to gamma chain deficiency [Available from: http://www.orpha.net/consor4.01/www/cgi-bin/Disease_Search.php?lng=EN&data_id=170&Disease_Disease_Search_diseaseGroup=X-linked-severe-combined-immunodeficiency--T--B-&Disease_Disease_Search_diseaseType=Pat&Disease(s)/group%20of%20diseases=T-B--severe-combined-immunodeficiency-due-to-gamma-chain-deficiency&title=T-B--severe-combined-immunodeficiency-due-to-gamma-chain-deficiency&search=Disease_Search_Simple.

277. Mucopolysaccharidosis type 1 [Available from: https://rarediseases.org/rare-diseases/mucopolysaccharidosis-type-i/.

278. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the Incidence, Prevalence, and Survival Outcomes in Patients With Neuroendocrine Tumors in the United States. JAMA Oncol. 2017;3(10):1335-42.

279. NICE. Guide to the methods of technology appraisal 2013 2013 [Available from: https://www.nice.org.uk/process/pmg9/chapter/the-reference-case.

280. McCabe C, Bergmann L, Bosanquet N, Ellis M, Enzmann H, von Euler M, et al. Market and patient access to new oncology products in Europe: a current, multidisciplinary perspective. Ann Oncol. 2009;20(3):403-12.

281. Ghinea N, Lipworth W, Kerridge I. Propaganda or the cost of innovation? Challenging the high price of new drugs. Bmj. 2016;352:i1284.

282. CMS: Innovative treatments call for innovative payment models and arrangements [press release]. CMS.gov2017.

283. Miller S. Gene Therapy Holds Great Promise, But Big Price 2017 [Available from: http://lab.express-scripts.com/lab/insights/drug-options/gene-therapy-holds-great-promise-but-big-price?hootPostID=6df8ced02008c379691d79549b166eaf&utm_source=STAT+Newsletters&utm_campaign=e308efdff8-EMAIL_CAMPAIGN_2017_09_20&utm_medium=email&utm_term=0_8cab1d7961-e308efdff8-149537785.

284. OECD. Sustainable access to innovative therapies - Online consultation 2017 [Available from: http://www.oecd.org/els/health-systems/sustainable-access-to-innovative-therapies-online-consultation.htm.

285. WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies [14/05/2017]. Available from: http://whocc.goeg.at/Glossary/PreferredTerms/External%20price%20referencing.

286. Rémuzat C, Urbinati D, Mzoughi O, El Hammi E, Belgaied W, Toumi M. Overview of external reference pricing systems in Europe. Journal of market access & health policy. 2015;3:10.3402/jmahp.v3.27675.

287. OECD. Pharmaceutical Pricing Policies in a Global Market. oecd, editor2008.

288. Liozua S, Hinterhuberb A, Bolanda B, Perellia S. The conceptualization of value-based pricing in industrial firms. Journal of Revenue and Pricing Management. 2011;11(1):12-34.

289. Ognyanova D, Zentner A, Busse R. Pharmaceutical reform 2010 in Germany. 2011. Contract No.: 1.

290. Motola D, De Ponti F, Poluzzi E, Martini N, Rossi P, Silvani MC, et al. An update on the first decade of the European centralized procedure: how many innovative drugs? Br J Clin Pharmacol. 2006;62(5):610-6.

291. Paris V, Belloni A. Value in Pharmaceutical Pricing. Paris; 2013.

292. Deloitte. Impact of austerity on European pharmaceutical policy and pricing. 2013.

293. Cameron A, Hill S, Whyte P, Ramsey S, Hedman L. WHO guideline on country pharmaceutical pricing policies Geneva: World Health Organization2013 [07/05/2017]. Available from: http://apps.who.int/iris/bitstream/10665/153920/1/9789241549035_eng.pdf?ua=1.

294. Hollis A. Sustainable Financing of Innovative Therapies: A Review of Approaches. Pharmacoeconomics. 2016;34(10):971-80.

295. Vogler S, Zimmermann N, Habl C, Piessnegger J, Bucsics A. Discounts and rebates granted to public payers for medicines in European countries. Southern Med Review. 2012;5(1):38-46.

296. Towse A, Garrison LP, Jr. Can't get no satisfaction? Will pay for performance help?: toward an economic framework for understanding performance-based risk-sharing agreements for innovative medical products. Pharmacoeconomics. 2010;28(2):93-102.

297. Barinaga G, Chambers MC, El-Othmani MM, Siegrist RB, Saleh KJ. Affordable Care Organizations and Bundled Pricing: A New Philosophy of Care. The Orthopedic clinics of North America. 2016;47(4):707-16.

298. Hussey PS, Ridgely MS, Rosenthal MB. The PROMETHEUS bundled payment experiment: slow start shows problems in implementing new payment models. Health Aff (Millwood). 2011;30(11):2116-24.

299. Korda H, Eldridge GN. Payment incentives and integrated care delivery: levers for health system reform and cost containment. Inquiry. 2011;48(4):277-87.

300. Robinson JC. Value and payment for oncology in the United States. Ann Pharm Fr. 2013;71(5):285-90.

301. Jain SH, Shrank WH. The CMS Innovation Center: delivering on the promise of payment and delivery reform. J Gen Intern Med. 2014;29(9):1221-3.

302. A Roadmap To Strategic Drug Pricing [Internet]. 2016. Available from: http://www.ey.com/Publication/vwLUAssets/ey-in-vivo-a-road-map-to-strategic-drug-prices-subheader/$FILE/ey-in-vivo-a-road-map-to-strategic-drug-prices-subheader.pdf.

303. Greenapple R. Rapid expansion of new oncology care delivery payment models: results from a payer survey. Am Health Drug Benefits. 2013;6(5):249-56.

304. Shih T, Chen LM, Nallamothu BK. Will Bundled Payments Change Health Care? Examining the Evidence Thus Far in Cardiovascular Care. Circulation. 2015;131(24):2151-8.

305. Bundled payment NAHU Education Foundation [Available from: https://nahueducationfoundation.org/toolkit/Infographics.cfm.

306. White C, Chan C, Huckfeldt PJ, Kofner A, Mulcahy AW, Pollak J, et al. Specialty Payment Model Opportunities and Assessment: Oncology Simulation Report. Rand health q. 2015;5(1):12.

307. Gavious A, Greenberg D, Hammerman A, Segev E. Impact of a financial risk-sharing scheme on budget-impact estimations: a game-theoretic approach. Eur J Health Econ. 2014;15(5):553-61.

308. Jarosławski S, Toumi M. Market access agreements for pharmaceuticals in Europe: diversity of approaches and underlying concepts. BMC Health Serv Res. 2011;11:259-.

309. Anastasaki E, Colasante W, Imbeah-Ampiah R. PHP30 CAN PRICING SCHEMES IMPROVE MARKET ACCESS FOR INNOVATIVE HIGH PRICED DRUGS? Value Health.14(3):A17.

310. Walzer S, Droeschel D, Shannon R. Which Risk Share Agreements are Available and are Those Applied In Global Reimbursement Decisions? Value Health. 2015;18(7):A568.

311. Aggarwal S, Topaloglu H, Messenger M. Novel Reimbursement Models For Cancer Drug Market Access (2010-2013). Value Health.16(3):A153.

312. Morgan SG, Vogler S, Wagner AK. Payers' experiences with confidential pharmaceutical price discounts: A survey of public and statutory health systems in North America, Europe, and Australasia. Health Policy. 2017;121(4):354-62.

313. Levy M, Rizansky Nir A. The pricing of breakthrough drugs: theory and policy implications. PLoS ONE. 2014;9(11):e113894.

314. Messori A. Application of the Price-Volume Approach in Cases of Innovative Drugs Where Value-Based Pricing is Inadequate: Description of Real Experiences in Italy. Clin Drug Investig. 2016;36(8):599-603.

315. Barry M, Tilson L. Reimbursement of new high cost drugs--funding the unfundable? Ir Med J. 2010;103(5):133.

316. Toumi M, Zard J, Duvillard R, Jommi C. Médicaments innovants et contrats d'accès au marché. Ann Pharm Fr. 2013;71(5):302-25.

317. Fellows GK, Hollis A. Funding innovation for treatment for rare diseases: adopting a cost-based yardstick approach. Orphanet J Rare Dis. 2013;8:180.

318. Persson U, Svensson J, Pettersson B. A new reimbursement system for innovative pharmaceuticals combining value-based and free market pricing. Appl Health Econ Health Policy. 2012;10(4):217-25.

319. Montazerhodjat V, Weinstock DM, Lo AW. Buying cures versus renting health: Financing health care with consumer loans. Sci Transl Med. 2016;8(327):327ps6.

320. Zettler PJ, Fuse Brown EC. The challenge of paying for cost-effective cures. Am J Manag Care. 2017;23(1):62-4.

321. Philipson T. Medical Breakthroughs And Credit Markets. Forbes2014.

322. Gottlieb S CT. Establishing new payment provisions for the high cost of curing disease 2014 [

323. Carr DR, Bradshaw SE. Gene therapies: the challenge of super-high-cost treatments and how to pay for them. Regen Med. 2016;11(4):381-93.

324. Meghani A, Basu S. A Review Of Innovative International Financing Mechanisms To Address Noncommunicable Diseases. Health Aff (Millwood). 2015;34(9):1546-53.

325. Kleinke JD, McGee N. Breaking the Bank: Three Financing Models for Addressing the Drug Innovation Cost Crisis. Am Health Drug Benefits. 2015;8(3):118-26.

326. Beauliere A, Le Maux A, Trehin C, Perez F. Access to antiretroviral treatment in developing countries: Which financing strategies are possible? Rev Epidemiol Sante Publique. 2010;58(3):171-9.

327. Jack A. Which way now for the Cancer Drugs Fund? BMJ : British Medical Journal. 2014;349.

328. Mayor S. New "managed access" process for Cancer Drugs Fund to go ahead, NHS England confirms. Bmj. 2016;352.

329. Lu CY. PHP188 Funding the Unfundable: The Australian Approach for Specialty Pharmaceuticals. Value Health.15(7):A322.

330. Barry M, Tilson L. Reimbursement of new high cost drugs--funding the unfundable? Ir Med J. 2010;103(5):133.

331. Proach J, Black J, Cromer K, Winters D. EXPLORING ALTERNATIVE PAYMENT METHODOLOGIES FOR INNOVATIVE, EXPENSIVE TREATMENTS: WHAT IS NEEDED TO TRIGGER A CHANGE FROM THE CURRENT UPFRONT PAYMENT SYSTEM? Value Health.19(3):A258.

332. Klemp M, Fronsdal KB, Facey K. What principles should govern the use of managed entry agreements? Int J Technol Assess Health Care. 2011;27(1):77-83.

333. Megerlin F. [Conditional pricing for innovative medicines in France: stop telling about risk-sharing!]. Ann Pharm Fr. 2013;71(5):291-301.

334. Long G, Mortimer R, Sanzenbacher G. Evolving provider payment models and patient access to innovative medical technology. J Med Econ. 2014;17(12):883-93.

335. Malik NN. Pay-for-performance pricing for a breakthrough heart drug: learnings for cell and gene therapies. Regen Med. 2016;11(3):225-7.

336. Macaulay R. Managed Access Agreements: A New Model Pathway for The Reimbursement of Non-Oncology Drugs in England Approved Under European Adaptive Pathways? Value Health.19(7):A505.

337. Fuller RL, Goldfield N. Paying for On-Patent Pharmaceuticals: Limit Prices and the Emerging Role of a Pay for Outcomes Approach. J Ambul Care Manage. 2016;39(2):143-9.

338. De Rosa M, Martini N, Ortali M, Esposito I, Roncadori A. An Innovative Cloud-Based Platform for Implementing Performance-Based Risk-Sharing Arrangements (Pbrsas) in Oncology Settings. Value Health.18(3):A273.

339. Dranitsaris G, Dorward K, Owens RC, Schipper H. What is a new drug worth? An innovative model for performance-based pricing. Eur J Cancer Care (Engl). 2015;24(3):313-20.

340. Garrison LP, Jr., Carlson JJ, Bajaj PS, Towse A, Neumann PJ, Sullivan SD, et al. Private sector risk-sharing agreements in the United States: trends, barriers, and prospects. Am J Manag Care. 2015;21(9):632-40.

341. Launois R, Navarrete LF, Ethgen O, Le Moine JG, Gatsinga R. Health economic value of an innovation: delimiting the scope and framework of future market entry agreements. Journal of market access & health policy. 2014;2.

342. Brennan TA, Wilson JM. The special case of gene therapy pricing. Nat biotechnol. 2014;32(9):874-6.

343. Messori A, De Rosa M, Pani L. Alternative pricing strategies for cancer drugs. Jama. 2015;313(8):857.

344. Bach PB. Indication-specific pricing for cancer drugs. Jama. 2014;312(16):1629-30.

345. Touchot N, Flume M. The payers' perspective on gene therapies. Nat biotechnol. 2015;33(9):902-4.

346. Edlin R, Hall P, Wallner K, McCabe C. Sharing risk between payer and provider by leasing health technologies: an affordable and effective reimbursement strategy for innovative technologies? Value Health. 2014;17(4):438-44.

347. Stafinski T, McCabe CJ, Menon D. Funding the unfundable: mechanisms for managing uncertainty in decisions on the introduction of new and innovative technologies into healthcare systems. Pharmacoeconomics. 2010;28(2):113-42.

348. Basu A, Subedi P, Kamal-Bahl S. Financing a Cure for Diabetes in a Multipayer Environment. Value Health. 2016;19(6):861-8.

349. OECD. New Health Technologies Managing Access, Value and Sustainability: Managing Access, Value and Sustainability2017. 231 p.

350. Health Impact Fund [Available from: http://healthimpactfund.org/publications/.

351. Marsden G, Towse A, Pearson SD, Dreitlein B, Henshall C. Gene Therapy: Understanding the Science, Assessing the Evidence, and Paying for Value. https://www.ohe.org/publications/gene-therapy-understanding-science-assessing-evidence-and-paying-value: ICER; 2017.

352. Garau M, Mestre-Ferrandiz J. Access Mechanisms for Orphan Drugs: A Comparative Study of Selected European Countries. OHE Briefing. 2009;52.

353. Montgomery B. Review of Access to New Medicines. 2016.

354. Prasad V, Mailankody S. The UK Cancer Drugs Fund Experiment and the US Cancer Drug Cost Problem: Bearing the Cost of Cancer Drugs Until It Is Unbearable. Mayo Clin Proc. 2016;91(6):707-12.

355. Triggle N. Cancer Drugs Fund 'huge waste of money' BBC News2017 [Available from: http://www.bbc.com/news/health-39711137.

356. Cohen D. Most drugs paid for by £1.27bn Cancer Drugs Fund had no "meaningful benefit". Bmj. 2017;357.

357. Toumi M. Introduction to Market Access for Pharmaceuticals. 1 ed2017 23 January 2017.

358. EMA. Early dialogue with regulators and HTA bodies 2016 [Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/03/news_detail_002499.jsp&mid=WC0b01ac058004d5c1.

Appendixes

APPENDIX I

Abstracts of presented posters

1. Market access of ATMPs: Overview and expected challenges

Hanna E1, Tavella F2, Rémuzat C1, Auquier P3, Toumi M4
1Creativ-Ceutical, Paris, France, 2Creativ-Ceutical, London, UK, 3Université de la Méditerranée,Marseille, France, 4Aix-Marseille University, Marseille, France

Objectives: Advanced therapy medicinal products (ATMPs) are a class of innovative and regenerative therapies. As of May 2015, only 5 ATMPs were granted a marketing authorisation (MA) in European Union (EU): three cell therapies, Provenge® (for advanced prostate cancer), Chondrocelect® and MACI® (for cartilage defects); one tissue engineering product, Holoclar® (for damaged cornea); and one gene therapy, Glybera®(for lipoprotein lipase deficiency). The aim of this study was to review the ATMPs assessments by EU HTA bodies.
Methods: EU big 5 HTA body websites were searched for their decisions on ATMPs: France (HAS), UK (NICE, SMC), Italy (AIFA and regions), Spain (MSSSI and regions), Germany (IQWiG, G-BA). Grey literature was also searched for further details.
Results: Chondrocelect® was only assessed in Spain and France; reimbursement was granted in Spain, rejected in France as efficacy/ adverse effects ratio had not been clearly established. Provenge® and MACI® were only assessed in the UK and Germany. NICE concluded that Provenge® did not demonstrate additional benefit nor cost-effectiveness against best supportive care; IQWiG/G-BA concluded "non-quantifiable" added benefit. MACI® was not recommended by NICE due to uncertainty in cost-effectiveness analysis and lack of long-term data, while its assessment has been suspended in Germany until further publication of randomised clinical trials. Only G-BA assessed Glybera® but could not conclude on its benefits due to limited data submitted by manufacturer. Holoclar® was approved in February 2015 but has not been assessed yet. Of note, MA for MACI® and Provenge®were suspended for commercial reasons.
Conclusions: Market access of ATMPs is challenging as the evidence available at market launch might not be sufficient to address the HTA agencies' expectations. Adaptive pathways for licencing and coverage of drugs might be a relevant approach for these medicines to reduce uncertainty through real-world data collection post-launch.

2. Advanced Therapy Medicinal Products may dramatically impact payers' budget

Hanna E1, Rémuzat C1, Auquier P2, Toumi M3
1Creativ-Ceutical, Paris, France, 2Université de la Méditerranée, Marseille, France, 3Aix-Marseille University, Marseille, France

Objectives: Advanced therapy medicinal products (ATMPs) are innovative therapies that encompass gene therapy, somatic cell therapy, and tissue engineered products. These therapies are expected to bring important health benefits, but also to substantially impact the pharmaceuticals budget. The aim of this study was to characterize ATMPs in development and discuss future implications in terms of market access.
Methods: Clinical trials were searched in EUdraCT, clinicaltrials.gov and ICTRP databases. Trials were classified by category of ATMPs as defined by European regulation EC N° 1394/2007, as well as by development phase and therapeutic area.

Results: 939 clinical trials investigating ATMPs were identified (85% ongoing, 15% completed). Majority of trials were in early stages (phase I, I/II, II: 92%; phase II/III, III: 8%). Per category of ATMPs, we identified 53.6% of trials for somatic cell therapies, 22.8% for tissue engineered products, 22.4% for gene therapies, and 1.2% for combined products (incorporating medical device). Therapeutic areas included cancer (24.8%), cardiovascular and blood diseases (21.5%), musculoskeletal disorders (10.5%), immune system and inflammation (9.4%), neurology (9.1%) and others. 47.2% of trials enrolled less than 25 patients. Due to complexity and specificity of ATMPs, new clinical trial methodologies are being considered (e.g. small sample size, non-randomised trials, single arm trials, surrogate endpoints, integrated protocols, and adaptive designs). Evidence generation post-launch will become unavoidable to address payers' expectations.
Conclusions: ATMPs represent a fast growing field of interest. Although most of the products are in early development phase, the combined trial phase and the potential to cure severe chronic conditions suggest that ATMPs may reach the market earlier than standard therapies. Targeted therapies opened up the way for new trial methodologies, from which ATMPs could benefit to get early access. ATMPs may be the next source of major impact on payers' drug budget.

3. The Failure of Pricing Policies in the European Union

Lee D1, Hanna E1, El Hammi E2, Rémuzat C1, Toumi M3
1Creativ-Ceutical, Paris, France, 2Evidenz, Tunis, Tunisia, 3Aix-Marseille University, Marseille, France
Background: Sofosbuvir, a breakthrough anti-HCV (hepatitis C virus) polymerase inhibitor, was first approved for early entry in 2012 in France. The product was granted a marketing authorisation in the United-States (US) and in the European Union (EU), by the end of 2013 and beginning of 2014, respectively. Shortly after licensing, most HTA bodies assessed sofosbuvir; they acknowledged a major additional benefit and find it cost-effective for a price around USD 80,000 in US and USD 55,000 in EU for a 12-week course treatment.
Discussion: Sofosbuvir price may have led to health insurances (HI) bankruptcy in EU and to substantially increase HI premium in US. In EU, politicians reacted through an orchestrated media campaign; manufacturer was called to clarify the gap between production cost and price, as if price cost was the drug industry model, while value-based pricing was in force. The most active campaign happened in France where members of parliament and Health Minister multiplied press releases and presence on media to dispute sofosbuvir price considered as scandalous, while compliant with French regulation. French Health Minister organized a European coalition to control its price. Under tremendous media, political and administrative pressure, the manufacturer accepted significant price decrease, early entry agreement in France and later in most EU countries. Following this saga, to ensure drug budget will remain under control, most EU countries issued regulation or law to cap drug budget expenditure for HCV.
Conclusion: This case highlights limit of current pricing policies which are unable to match affordability and drug prices. Even if cost effectiveness remains important information for efficiency assessment, sofosbuvir case confirms the inability of cost-effectiveness analysis to address affordability issue. Budget impact in supporting decision making will become more and more critical in the future.

4. **Comparison of the trends of orphan drugs designations and approvals in the United States and Europe in oncology**

Hanna E1, Korchagina D2, Toumi M1
1Faculté de Médecine, Laboratoire de Santé Publique, Aix-Marseille Université, Marseille, France, 2University of Paris-Sud, Paris, France

Objectives: Orphan drugs (OD) constitute a class of drugs that have been developed specifically to treat a rare medical condition referred to as "rare disease". In January 1983, the United States (US) implemented the Orphan Drug Act (ODA). The European orphan drugs regulation was implemented almost 20 years after the US regulation, in 16 December 1999. Our objective is to compare the number of oncology orphan drugs designated and approved in the European Union (EU) and US.
Methods: All designated OD were extracted from US FDA database and the European Medicines Agency (EMA) database. The oncology condition was selected in the 2 lists. Drugs with withdrawn orphan designation or market authorisation were excluded from the analysis. Different orphan designations granted for different indications for the same molecule were considered separate approvals. Then the numbers of designations and approvals by period of time were compared between EU and US. Results: In the US, 969 oncology drugs were orphan designated between 1984 and 2015, of which 122 are approved (12.59%). In EU between 2000 and 2015, 397 oncology products received OD designation of which 35 (8.81%) were approved. During the same period 823 where designated in US and 77 (9.35%) approved. Proportion of approvals was similar. Trends showed continuous sustained growth overtime in US for designation and approval. In EU after an initial catch up period (2000-2005) the growth was less marked.
Conclusions: This analysis supports the continuous gap between US and EU in the number of designated and approved oncology products, despite much longer data protection offered in EU. The difference is more driven by entrepreneurial attitude (more products filled and developed) in US than by the regulatory criteria for designation that are reasonably aligned or by the highest rejection rate in EU.

5. **Risk of discontinuation of advanced therapy medicinal products clinical trials**

Hanna E1, Rémuzat C2, Toumi M1
1Faculté de Médecine, Laboratoire de Santé Publique, Aix-Marseille Université, Marseille, France, 2Creativ-Ceutical, Paris, France

Objectives: Advanced Therapy medicinal products (ATMPs) constitute a class of innovative products that encompasses: gene therapy, somatic cell therapy and tissue engineered products (TEP). There is an increased investment of commercial and non-commercial sponsors in this field. Randomized clinical trials (RCT) generate data to prove the efficacy of a new therapy, but the discontinuation of RCTs wastes scarce resources. Our objective is to identify the number and characteristics of discontinued ATMPs trials in order to evaluate the rate of discontinuation.
Methods: We searched for ATMPs trials conducted between 1999 to June 2015 using three databases: Clinicaltrials.gov, the International Clinical Trials Registry Platform (ICTRP) and the EudraCT. We selected the ATMPs trials after elimination of duplicates. We identified the disease areas and the sponsors as commercial or non-commercial organization. We classified ATMPs by type and trial status: ongoing, completed, terminated, discontinued, and prematurely ended. Then we calculated the rate of discontinuation.
Results: 143 withdrawn, terminated or prematurely ended ATMPs clinical trials were identified between 1999 and June 2015 and 474 ongoing and completed clinical trials. Therefore, the rate of discontinuation of ATMPs trials is 23.17% similar to non-ATMPs drugs in development. The probability of discontinuation is respectively 27.35%,

16.28%, and 16.34% for cell therapies, gene therapies, and TEP. The highest discontinuation rate is for oncology (44%) followed by cardiology and immunology/inflammation (22.2%). It is almost the same for commercial and non-commercial sponsors (24%); Suggesting discontinuation may not be financially driven. Conclusions: No failure risk rate per development phase is available for ATMPs. Discontinuation rate may prove helpful when assessing expected net present value to support portfolio arbitration. These results carry limitation as the reason for discontinuation is unknown. Further research about the reasons of discontinuation and the risk of negative results is needed to inform manufacturers and investors decisions.

6. Advanced Therapy Medicinal Products for Alzheimer's disease will shrink the national health service budget

Hanna E1, Zhou J2, Cheng X3, Dorey J4, Aballéa S4, Auquier P1, Toumi M1
1Faculté de Médecine, Laboratoire de Santé Publique, Aix-Marseille Université, Marseille, France, 2Creativ-Ceutical, Beijing, China, 3Creativ-Ceutical, Hong Kong, Hong Kong, 4Creativ-Ceutical, Paris, France

Objectives: Advanced Therapy Medicinal Products (ATMPs) are therapies expected to cure, halt or slow progression of many disabling diseases among which Alzheimer's disease (AD). Stem cell therapies targeting AD are in development. Our objective is to evaluate ATMPs Drug budget impact (DBI) on Health Insurance (HI) in AD assuming various efficacy profiles.
Methods: A Markov model was developed to compare two strategies: Standard of care (SoC) and ATMPs for a representative cohort of AD patients over a 5-year period, with 1-month cycle-length. Model input data, SoC costs and quality-adjusted life year (QALY) data were derived from published sources. We assumed that one procedure allows achieving the outcome. Five efficacy scenarios were tested to evaluate the cost of ATMP procedures assuming an ICER threshold of 30,000£/ QALY. DBI was computed by multiplying the procedure cost by AD prevalence in the United Kingdom.
Results: In the first and second scenarios, 100% and 50% patients were cured respectively with a DBI of 72,132,071,000£ and 37,357,245,000£. In the third and fourth scenarios, probabilities of progression were reduced by 50% and 67% leading to respective DBI of 1,435,420,500£ and 1,895,457,500£. In the fifth scenario, patients did not progress further and the DBI was 2,839,051,000£.
Conclusions: About 1000 ATMPs are in development of which 65 already in phase III. These therapies are expected to cure, halt or significantly slow down the progression of chronic and severely disabling diseases. If these therapies successfully reach the market they will bring unprecedented clinical and social benefits to patients and the society. However they are likely to severely impact the National Health Service (NHS) budget thus threatening sustainability of the healthcare system. Without deep policy changes in the pharmaceutical interventions pricing, the sustainability of health systems in the EU Member States will be severely threatened.

7. Will stem cells for heart failure be the next sofosbuvir issue?

Hanna E1, Dorey J2, Aballéa S2, Auquier P1, Toumi M1
1Faculté de Médecine, Laboratoire de Santé Publique, Aix-Marseille Université, Marseille, France, 2Creativ-Ceutical, Paris, France

Objectives: Advanced Therapy Medicinal Products (ATMPs) are therapies expected to cure, halt or slow down the progression of many disabling diseases among which Heart Failure disease (HF). About 1000 ATMPs are in development of which 65 already in phase III. These therapies are expected to cure, halt or significantly slow down the progression of chronic and severely disabling diseases. Stem cell therapies targeting HF

are in development. Our objective is to evaluate ATMPs Drug budget impact (DBI) on Health Insurance (HI) in HF assuming various efficacy profiles.
Methods: A Markov model was developed to compare two strategies: Standard of care (SoC) and ATMPs for a representative cohort of HF patients over a 10-year period, with 1-month cycle-length. Model input data, SoC costs and quality-adjusted life-year (QALY) data were derived from published sources. We assumed that one procedure allows achieving the outcome. Five efficacy scenarios were tested to evaluate the cost of ATMP procedures assuming an ICER threshold of 50,000€ /QALY. DBI was computed by multiplying the procedure cost by HF prevalence in France.
Results: In the first and second scenarios, 100% and 50% patients were cured respectively with a DBI of 348,144,688,850€ and 192,523,977,243€ . In the third and fourth scenarios, probabilities of progression were reduced by 50% or 33% leading to respective DBI of 1,186,221,568€ and 1,606,499,643€ . In the fifth scenario, patients did not progress further and the DBI was 2,355,086,110€ . Conclusions: If ATMPs successfully reach the market, they will bring unprecedented clinical and social benefits to patients and society. However they are likely to severely impact the French health service budget thus threatening sustainability of the healthcare system. Without deep policy changes in the pharmaceutical interventions pricing, the sustainability of health system in the EU Member States will be severely threatened.

8. Future innovative therapies for Parkinson's disease may question sustainability of our health care system

Hanna E1, Ma F2, Cheng X3, Dorey J4, Aballéa S4, Auquier P1, Toumi M1
1Faculté de Médecine, Laboratoire de Santé Publique, Aix-Marseille Université, Marseille, France, 2Creativ-Ceutical, Beijing, China, 3Creativ-Ceutical, Hong Kong, Hong Kong, 4Creativ-Ceutical, Paris, France
Objectives: Advanced Therapy Medicinal Products (ATMPs) are therapies expected to cure, halt or slow down the progression of many disabling diseases among which Parkinson's disease (PD). Gene and cell therapies targeting PD are in development (E.g. AAV2-GAD gene therapy). Our objective is to evaluate ATMPs Drug budget impact (DBI) on Health Insurance (HI) in PD assuming various efficacy profiles.
Methods: A Markov model was developed to compare two strategies: Standard of care (SoC) and ATMPs for a representative cohort of PD patients over a 10-year period, with 6 month cycle-length. Model input data, SoC costs and quality-adjusted life-year (QALY) data were derived from published sources. We assumed that one procedure allows achieving the outcome. Five efficacy scenarios were tested to evaluate the cost of ATMP procedures assuming an ICER threshold of 30,000£/QALY. DBI was computed by multiplying the procedure cost by PD prevalence in the United Kingdom.
Results: In the first and second scenarios, 100% and 50% patients were cured respectively with a DBI of 11,202,449,878£ and 6,568,104,991£. In the third and fourth scenarios, probabilities of progression were reduced by 50% and 33% leading to respective DBI of 1,398,174,177£ and 722,816,403£. In the fifth scenario, patients did not progress further and the DBI was 4,165,812,990£.
Conclusions: About 1000 ATMPs are in development of which 65 already in phase III. These therapies are expected to cure, halt or significantly slow down the progression of chronic and severely disabling diseases. If these therapies successfully reach the market they will bring unprecedented clinical and social benefits to patients and society. However they are likely to severely impact the National Health Service (NHS) budget. Without deep policy changes in the pharmaceutical interventions pricing, the sustainability of health systems in the EU Member States will be severely threatened.

9. Advanced Therapies: Widening the gap between payers and regulators

Hanna E1, Rémuzat C2, Auquier P1, Toumi M1
1Faculté de Médecine, Laboratoire de Santé Publique, Aix-Marseille Université, Marseille, France, 2Creativ-Ceutical, Paris, France

Objectives: Advanced Therapy Medicinal Products (ATMPs) are innovative therapies including gene therapies, cell therapies, and tissue engineered products. These therapies are expected to halt or cure many chronic, disabling diseases. While European regulators tend to speed market access of such therapies through accelerated pathways (authorisation under exceptional circumstances, conditional marketing authorisation, accelerated assessment, adaptive pathways and PRIME), health technology assessment (HTA) bodies/payers are increasingly scrutinising the incremental value of these products. The study objective was to identify potential gap in the evaluation of ATMPs between payers and regulators in Europe.

Methods: A search was conducted in European Medicines Agency (EMA) website to identify ATMPs approved in Europe; HTA assessment of these ATMPs was reviewed for France, Germany and United Kingdom through HAS, IQWiG/G-BA, NICE and SMC websites.

Results: Seven ATMPs received a marketing authorisation (MA) in Europe until June 2016: Chondrocelect® (2009), Glybera® (2012), MACI® (2013)-MA suspended in 2014, Provenge® (2013)- MA withdrawn in 2015, Holoclar® (2015), Imlygic® (December 2015), Strimvelis® (May 2016). None of these ATMPs has been recommended for reimbursement by HTA bodies in the study scope. Only Chondrocelect® is reimbursed on a case-by-case basis in Germany after negotiation between hospital and appropriate regional health insurance. HAS did not recommend Chondrocelect® and Glybera® due to insufficient actual benefit. NICE considered that Provenge® was not cost-effective and did not meet the criteria for end-of-life consideration. Glybera® and Provenge® were rated as "nonquantifiable added benefit" by IQWiG/G-BA. Holoclar®, Imlygic® and Strimvelis® have not yet been assessed.

Conclusions: EMA is accelerating the regulatory pathways for innovative products whereas HTA bodies tend not to recommend ATMPs for reimbursement mainly because of immature data. Parallel advice may help harmonizing HTA and regulators' perspectives and provide manufacturers recommendations to achieve market access for ATMPs, while more than 900 ATMPs are in development.

10. A new accelerated early access process for diagnostics in France

Hanna E, Azaiez C, Auquier P, Toumi M
Faculté de Médecine, Laboratoire de Santé Publique, Aix-Marseille Université, Marseille, France

Objectives: The fast development of precision medicine led to fast development of new diagnostic tools. New diagnostics face a complex access process delaying potential benefit to patients. France put in place an accelerated access process (AAP) for innovative diagnostics with immature data. This study objective is to describe AAP and analyse its potential impact on development and patient access to innovative diagnostics.

Methods: We reviewed the French regulation for AAP called Référentiel des actes Innovants Hors Nomenclature (RIHN): Instruction N° DGOS/ PF4/2015/258, July 31st, 2015, and analysed potential implications on diagnostics manufacturers.

Results: In July 2015, the General directorate of health services (DGOS) established RIHN to support ongoing development of innovative laboratory medicine and pathology diagnostics. RIHN support evaluation of innovative diagnostics in "real life" before HTA assessment and pricing is issued. Payers support manufacturers by co-funding studies to collect clinical and economic data to prove efficacy and cost-effectiveness. Early dialogue

with payers helps to increase diagnostic acceptability and chances of reimbursement. In parallel to study support, RIHN ensures a temporary reimbursement for 3 years; after what, there are 3 options: positive evaluation by DGOS and dossier transmission to HAS, negative evaluation and test withdrawal, unassessable evidence due to limited data and extension of the inclusion in RIHN for 2 additional years. RIHN endorsed tests are reimbursed on yearly basis to hospitals, retrospectively according to number of tests performed.
Conclusions: After the Temporary Authorisations for Use (ATU) and "forfait innovation", RIHN constitutes the third pillar to support early access to innovation in France. It aims to remove hurdles and facilitate access of innovative laboratory medicine and pathology tests onto French market by providing temporary funding. French payers are moving from a "see-to-pay" to "pay-to-see" strategy. France might now be considered an attractive market for launching new and innovative diagnostics.

11. Relevance of indirect comparison in HAS assessment

Hanna E1, Rémuzat C2, Auquier P1, Jadot G3, Toumi M1
OBJECTIVES: "Head-to-head" trial or direct comparison is the classical approach considered as gold standard to compare the efficacy, safety and additional overall benefit of 2 treatments. Indirect comparison may in some cases be the only option to compare interventions. Although, in theory, French health authority (HAS) accepts the indirect comparisons and a guideline for indirect comparison is published, it is not clear if they are accepted in practice. The aim of this study is to identify the number of indirect comparisons in oncology as well as their acceptability by HAS.
METHODS: HAS reports published between 01/01/2012 and 31/12/2016 for oncology products were extracted from HAS website. Only initial submission reports were included in this study. Generics and biosimilar products assessments were excluded. Then, indirect comparisons were identified in each report as well as the opinion of HAS on these comparisons when available.
RESULTS: 292 reports for oncology products were extracted among which 67 were included in this study. Indirect comparisons were submitted only for 8 of the 67 products in addition to the head-to-head randomized clinical trials. HAS considered that indirect comparisons have a minor impact and they were not considered actually in the final assessment. Consistently, HAS questioned the value of these indirect comparisons because they were thought to have limitations due to period differences, potential heterogeneity of studies (population and patients' management etc) as well as potential population selection that may be very different even though those heterogeneity criticisms were not robustly documented.
CONCLUSIONS: The use of indirect comparison is becoming unavoidable as it is almost impossible to generate comparative head-to-head data for all relevant interventions. Despite some products indirect comparisons availability for other HTA agencies, they are not filed to HAS. When filed they happen to have very little impact on the HAS assessment.

12. Funding of gene therapies in Europe & the United States

Hanna E1, Rémuzat C2, Auquier P1, Jadot G3, Toumi M1
OBJECTIVES: Gene therapies (GT) are promising treatments able to potentially cure chronic and disabling diseases after single or short-course administration. Such products deliver long-term benefits after administration. The short-course administration associated to long-term high value lead to high upfront costs that challenge the sustainability of national health insurance systems. As an important number of gene therapies are expected to reach the market, finding a sustainable funding model for GT is needed. The aim of this study is to identify potential funding

models for gene therapies in the large 5 EU countries: Germany, United Kingdom, France, Italy, and Spain as well as US.
METHODS: A literature review was conducted in PubMed, congress abstracts, Health Technology Assessment bodies' websites and grey literature.
RESULTS: There is no specific path for GT pricing and reimbursement. However, several methodologies have been proposed to set GT price. Four funding models were proposed: "technology leasing reimbursement strategy", high-cost drug mortgages, high-cost drugs reinsurance, and high-cost drug patient rebates. Some authors suggested that this may jeopardize the future health insurance resources and cannot constitute a generalizable model; they proposed discounts according to the turnover. Other authors proposed constraint optimization models for GT pricing, while others considered those models inapplicable to US as patients change health plan regularly thus disconnecting initial investment and future value.
CONCLUSIONS: Current pricing models based on unit price are too one-dimensional for the future needs of the market assuming GT successful arrival to the market. Performance driven managed entry agreements are unlikely to address the short course treatment and long-term value. Many proposed models may be inadequate; they may be too costly on long term or lead to inappropriate return on investment. While GT started reaching the market, no clear research enlightens payers on optimal funding models.

13. Do French health economics and clinical HTA committees have coherent appraisals of clinical trials?

Hanna E1, Rémuzat C2, Jadot G3, Toumi M1
OBJECTIVES: In France, the Economic and Public Health Assessment Committee (CEESP) and the transparency committee (TC) are 2 independent committees affiliated to the French health authority (Haute Autorité de Santé: HAS). TC assesses medicinal products clinical evidences and provides recommendations on reimbursement for public authorities whereas CEESP provides recommendations on health economics evaluations. These 2 committees operate in parallel without any coordination or communication of information which constitutes a specificity of the French system. The aim of this study was to evaluate the consistency in evaluating clinical trials between CEESP and TC.
METHODS: All available CEESP published opinions were searched in HAS website, then the TC opinions for the same products were downloaded. Major comments on clinical trials were extracted from both reports by two different analysts. Comments were classified as limited number of included patients (<50), non-comparative trials, and insufficient data based on CEESP opinion and then compared to TC opinion.
RESULTS: Twenty published CEESP opinions were identified. Aside health economics comments, CEESP had no comments on clinical trials in 11 reports, while TC identified limitations in 8 reports. In 2 CEESP reports insufficient data was claimed, 4 had a limited number of included patients and 3 non-comparative trials. Out of the 9 comments reported by CEESP, 8 were mentioned also on TC opinions. However, TC presented more detailed evaluation and discussion of all the product clinical trials.
CONCLUSIONS: A strong coherence in the assessment of clinical trials can obviously be concluded from this comparison. These results raise the issue of effort and work duplication due to the parallel and independent work between the 2 committees. On the other hand, this coherence reveals the homogeneity of the HAS assessment culture.

14. GENE THERAPIES DEVELOPMENT: SLOW PROGRESS AND PROMISING PROSPECT

Hanna E1, Rémuzat C2, Auquier P1, Toumi M1
OBJECTIVES:In 1989, the concept of human gene therapies has emerged with the first approved human gene therapy trial of Rosenberg et al. Gene therapies are considered as

promising therapies applicable to a broad range of diseases. The objective of this study was to review the descriptive data on gene therapy clinical trials conducted worldwide between 1989 and 2015, and to discuss potential success rates of these trials over time and anticipated market launch in the upcoming years.
METHODS:A publicly available database, 'Gene Therapy Clinical Trials Worldwide', was used to extract descriptive data on gene therapy clinical trials: (1) number of trials per year between 1989 and 2015; (2) countries; (3) diseases targeted by gene therapies; (4) vectors used for gene delivery; (5) trials status; (6) phases of development.

RESULTS: Between 1989 and 2015, 2,335 gene therapy clinical trials have been completed, were ongoing or approved (but not started) worldwide. The number of clinical trials did not increase steadily over time; it reached its highest peak in 2015 (163 trials). Almost 95% of the trials were in early phases of development and 72% were ongoing. The United States undertook 67% of gene therapy clinical trials. The majority of gene therapies clinical trials identified targeted cancer diseases.
CONCLUSIONS: The first gene therapy was approved in the European Union in 2012, after two decades of dashed expectations. This approval boosted the investment in developing gene therapies. Regulators are creating a specific path for rapid access of those new therapies, providing hope for manufacturers, healthcare professionals, and patients. However, payers are increasingly scrutinizing the additional benefits of the new therapies. The potential budget impact may become the actual hurdle for gene therapies, leading to restricted access and lost opportunities for many patients.

15. Could healthcoin be a revolution in healthcare?

Hanna E1, Remuzat C2, Auquier P1, Dussart C3, Toumi M1
1Aix-Marseille University, Marseille, France, 2Creativ-Ceutical, Paris, France, 3Lyon 1 University, Lyon, France
OBJECTIVES: Blockchain consists of a shared database used to maintain a continuously growing list of transactions, called blocks. Blockchain technology has started in 2008 with the first decentralized digital currency "Bitcoin". Bitcoin is a cryptocurrency and a digital payment system that can be exchanged for other currencies or products. New potential uses of blockchain are under investigation among which its application in healthcare "healthcoin". Our aim was to review the available information on healthcoin to gain a better understanding of this concept and its applicability.
METHODS: A literature review was conducted in Pubmed and the grey literature using the keywords: Healthcoin, blockchain, healthcare, financing, breakthrough therapies. Articles in French and English were included and no timelines restrictions were applied.
RESULTS: Founded in 2016 by Diego Espinosa and Nick Gogerty, healthcoin was the first blockchain based platform for rewarding prevention of diabetes. Users submit their biomarkers (hemoglobin A1c) into the blockchain that automatically calculates the improvement and awards the patient digital tokens: "healthcoins". For each healthcoin earned, a tax break can be offered by the government; a discount on fitness brands can be offered to reward patients. This same currency concept was adapted by Basu et al. 2016 as a new financing method for breakthrough therapies for diabetes. It converts the incremental benefits produced by the novel therapy to a common numeraire such as life years gained. It is a currency that could be traded between the private payers and Medicare in the United States, rewarding the former to invest in breakthrough therapies that provide important efficacy for patients before the age of 65.
CONCLUSIONS: Healthcoin may potentially constitute a revolution for the healthcare sector. Healthcare industry can share and store information transparently through healthcoin. Further studies to assess the feasibility of healthcoin payments may be interesting for payers and decision makers.

16. Potential funding sources for breakthrough therapies

Hanna E1, Remuzat C2, Auquier P1, Dussart C3, Toumi M1
1Aix-Marseille University, Marseille, France, 2Creativ-Ceutical, Paris, France, 3Lyon 1 University, Lyon, France

OBJECTIVES: Chronic diseases constitute a worldwide public health issue with important clinical unmet needs. Novel breakthrough therapies such as advanced therapy medicinal products (ATMPs) are in development to fulfill those unmet needs. ATMPs are expected to have high upfront costs. A key remaining question is the funding options of these new high cost therapies giving the large target population, and therefore the large budget needed. The aim of this study was to identify new funding sources for novel breakthrough therapies.
METHODS: A systematic review was conducted in Ovid Medline and Embase to identify innovative funding sources for novel therapies. Studies published between January 2000 and January 2017, written in English or French were included.
RESULTS: Four funding sources were mainly proposed in the literature: pooled funding, international transaction taxes, front-loading and debt reduction. Pooled funding is a combination of funding from multiple groups or multiple payers (in the case of the United States) to pay for a specific therapy. Another suggested solution is collecting funds through placing taxes and levies on specific transactions (e.g. plane tickets). Funds could also be provided through frontloading mechanism; some donors offer aids and resources to fund novel therapies like the International Finance Facility for Immunization that provided stable funding to achieve immunization goals. Furthermore, an international cooperation by debt reduction can constitute another solution, where a country creditor agrees to write off debt for a country debtor if the latter commits counterpart funding to an account that had been approved for a breakthrough therapy.
CONCLUSIONS: The suggested methods may be a potential source of additional funds for novel advanced therapies. Those methods have already been used for communicable diseases. A worldwide cooperation is needed to adapt these methods for non-communicable diseases in order to ensure the patient access to innovative therapies while maintaining the health care system sustainability.