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Barriers for the evaluation of advanced therapy medicines and their translation to clinical practice: Umbrella review

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ABSTRACT

Advanced therapy medicinal products (ATMPs) are a fast-growing field of medicine with wide potential application. Nevertheless, so far, only 19 have obtained European Union (EU) marketing authorisation and only 13 of these have translated successfully into clinical practice. This study conducts an umbrella review to identify the main barriers for the evaluation of ATMPs and their translation into clinical practice across the development lifecycle. 71 systematic reviews were included, of which 50 dealt primarily with effectiveness and safety, 13 with translation from pre-clinical to human subjects. Others dealt with economic issues and translation from health technology assessment to market access. The literature highlights the importance of synergistic research groups or networks that collaborate across the *in-vitro* science, preclinical and clinical investigation phases, and the role of private investor capital and public-private collaborations. Most ATMPs reviewed seem to have a favourable safety profile although considerable uncertainties remain. Randomised controlled trials are not always feasible in these patient groups. Greater sharing of data is recommended, both at preclinical and post-marketing real world evidence. There are considerable variations between EU countries in how they regulate hospital exemption for ATMPs, and this can lead to inequitable access for patients.

1. Introduction

Advanced therapy medicinal products (ATMPs) include gene therapies, substantially modified somatic cell therapies, tissue-engineered products and combined ATMPs [1]. Their medical indications cover a wide spectrum of human pathologies, such as cancer, neurodegenerative diseases, cardiovascular or tissue damage [2]. By the end of 2021, 19 ATMPs had been authorised by the European Medicines Agency (EMA), 6 of which with conditional approval (CMA) and 2 under exceptional circumstances (ECMA) [3] (See supplementary Table S1: ATMP with marketing authorization and withdrawn). It has been estimated that 1100 biotech and pharma companies are developing these types of products [4] and forecasts suggest that between 10 and 20 new ATMPs could be approved per year by 2025 [4]. Over 1000 clinical trials on ATMPs were underway in 2019, of which 152 were in Phase 3 [5], and in 2020 249 clinical trials were in development or completed on ATMPs in the *clinicaltrails.gov* database [6].

However, regulatory approval does not guarantee commercial success, and 6 ATMPs have been withdrawn from the market in Europe by 2022, for reasons that are not always clear [3]. Industry analysts suggest various factors, including unfavourable interim data from Phase III trials (Zalmoxis) [7], failure to obtain reimbursement in key European health systems (Glybera) [8] multiplicity of criteria for health technology assessment (HTA) for adoption in different European countries [8], complex administration and manufacturing (Provenge) [9], and competition from cheaper alternatives (MACI, Provenge) [10,11].

The path from basic research to healthcare delivery is often termed "translation" but this term is used in diverse ways and hence often leads to confusion. Woolf et al. [12] distinguishes between T1 translation, the enterprise of translating pre-clinical (animal) research into clinical

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(first-in-human) studies, and T2 translation, which refers to moving from clinical trials to healthcare practice.

ATMPs encounter barriers to translation in both T1 and T2 [13] (Fig. 1). With this in mind, EMA created the Committee for Advanced Therapies (CAT). The CAT works together with other EMA committees in the regulatory evaluation and surveillance of ATMPs, as well as initiatives for unmet need, such as PRIME [14]. There are differences in evidence requirements between regulatory and HTA agencies. EMA marketing authorisation is based on the benefit-risk ratio, manufacturing quality and level of unmet medical need, whereas HTA agencies are tasked with assessing comparative efficacy, budget impact, and/or the cost-effectiveness of a therapy [7]. However, HTA agencies in each country apply different criteria and it has been suggested that such assessments do not always take account of the special character of ATMPs [5].

In the case of ATMPs, European regulation establishes an alternative route to patient access without EMA marketing authorization [15]- the hospital exemption (HE). Under the supervision of the national competent authorities in each country, HE allows the non-routine use of an ATMP for patients who lack therapeutic alternatives without evaluation by the usual EMA and national HTA agencies. These authorisation rules differ from country to country, which can lead to inequalities in access to therapies between patients in different countries [16].

There have been several previous reviews of the challenges and incentives faced by stakeholders of ATMPs at the preclinical, clinical and clinical practice phases in the development pathway and from distinct perspectives: discontinuation of clinical trials [17], accelerated regulatory assessment [14], use of non-randomised studies in regulatory approval [18], horizon scanning [19], methods for HTA [20], methods for economic evaluation in HTA [21,22], ethics in HTA [11], and financing ATMP [23].

This paper adds to this literature an umbrella review, that is, a review of the previous systematic reviews (SR). We aim to collect all the evidence from existing reviews to give a high-level overview. This approach is considered especially useful and pragmatic when there are multiple interventions of interest [24]. Our aims are to summarise, according to the literature, the main barriers for the evaluation of ATMPs and their translation into practice across all the points in the development pathway and all the different pathologies.

We define "a barrier" as a statement made by the authors of the SR that represents an obstacle to granting a positive recommendation by regulators or HTA agencies and/or to facilitating its translation into clinical practice. If a barrier exists, it does not necessarily mean that it should be removed. Control mechanisms protect patients from unnecessary harm and ensure that therapies are effective, but they should not prevent or slow down access to medicines with a favourable benefit-risk and cost-effectiveness profile.

The article is structured as follows. The methodology section sets out the search strategy and the umbrella review methodology. The results section describes the characteristics of the included studies and barriers to evaluation or translation. In the discussion part, we comment on the implications of the results for the regulation, evaluation and translation of these medicines.

2. Methodology

2.1. Review protocol

The protocol of this review was registered in the PROSPERO (*International Prospective Register of Systematic Reviews)* database under reference CRD42021232943. The review was conducted according to the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA) [25] statement.

2.2. Search strategy

For the review of the scientific evidence, a bibliographic search was carried out in the reference databases Medline (without Revisions, Ovid MEDLINE Epub Ahead of Print March, Ovid MEDLINE Daily Update March, PubMed online first ahead of print), Embase (ExcerptaMedica-DataBase), Cochrane Library (Cochrane Review Database) and INAHTA (International HTA Database), WOS (SCI Science Citation Index).

Controlled language (descriptors) and free terminology (*advanced therapy, cell-and tissue-based therapy, genetic therapy, tissue engineering*) were used to identify the studies, adapting the initial strategy to the syntax of each database. These searches were limited to systematic reviews or meta-analysis, by language (Spanish or English), and by time limit of the last six years (2014 to August 2020) (See supplementary Table S2: search strategy Medline). Secondary manual searches of the bibliography of the articles obtained in the strategies described above were also carried out in order to identify additional studies. Finally, a search for synthesis documents (e.g. HTA reports) was carried out.

Grey literature and documents published in other sources, such as abstracts, reports, documents from scientific societies, official bodies or state and international agencies, portals, metasearch engines and databases were consulted. The resources consulted were: Tripdatabase, NICE Evidence Search, Guide gray and Epistemonikos. For this, free text terminology was used with a 2014-August 2020 date limit. These databases were included to enable the detection of possible studies of interest for this review (regulation, patient care information, research reports, technical reports, patents, scientific society documents) which might not be found in the standard databases.

2.3. Inclusion and exclusion criteria

Systematic reviews were included for safety, efficacy, effectiveness, cost, cost-effectiveness, patient perceptions, reporting standards, regulatory issues or translation, of one or more advanced therapies. Therapies in either the pre-clinical, clinical or post-marketing phases were included. Protocols of SR and SR that mainly dealt with therapies that were not ATMP were excluded.

2.4. Data extraction

Studies identified in the search were assessed by two reviewers independently (LAC, APP) according to the pre-established inclusion and exclusion criteria, first by title and abstract and then by full text. Discrepancies between reviewers were resolved by discussion and consensus. The extracted data included the pathology, the category of the therapy (gene, cell or tissue), the names of the therapies, the number of studies and the type of studies included in the SR (pre-clinical study,

Fig. 1. The path from basic research to clinical practice, and gaps in translation T1 and T2 (adapted from Becla et al. [13]). Abbreviations: *HTA* health technologies assessment.

randomised-controlled trials only or other clinical study), the number of distinct therapies in the SR, the principal outcome measure of the SR (efficacy, safety, economic, translation T1 or translation T2) and the main barriers for evaluation or translation highlighted by the authors.

Authors use diverse adjectives to refer to the magnitude and certainty of benefits or risks ("paradigm-shifting", "promising" and so on). To facilitate comparison between studies, We classify the author's estimation of the added therapeutic benefit broadly following the typology of the German HTA agency [26]: major (referring to a sustained increase in survival, long-term freedom from serious symptoms or substantial improvement in quality of life); considerable (moderate improvement in survival or alleviation of symptoms); minor or promising (that could include results in a surrogate outcome); no difference; or unquantifiable. It is vital that the concept of added therapeutic benefit recognises quality of life and length of life equally, given that many of the diseases treated by ATMP (See Supplementary Table S1) have severe, debilitating symptoms (such as knee joint damage, anal fistula or loss of sight) but do not affect survival.

2.5. Quality of the studies included

The quality of the included studies was assessed using the AMSTAR-2 tool [27] for systematic reviews. High quality refers to zero or one non-critical weakness, moderate refers to more than one non-critical weakness, low means one critical flaw with or without non-critical weaknesses and critically low means more than one critical flaw with or without non-critical weaknesses.

3. Results

A total of 945 studies were identified in the initial search. After eliminating duplicates, 717 potentially relevant articles were obtained. They were filtered by title and abstract by two independent researchers, obtaining a total of 176 relevant studies, in case of disagreements were resolved by consensus of the researchers. After filtering by full text, 71 studies were finally included (Fig. 2) (See supplementary Table S3: Studies included). No systematic reviews (conducted according to a valid protocol) were found in the HTA agency reports.

3.1. Characteristics of the included studies

Of the 71 systematic reviews included in the review: 8(11%) dealt with gene therapy medicinal products (GMTPs), 30 (42%) dealt with cell therapy medicinal products (CTMPs), 24 (34%) dealt with tissue-engineered products (TEPs) and 9 (13%) dealt with several types of ATMPs, see Table 1 and Fig. 3. Regarding the quality of the included studies, according to the AMSTAR-II tool [27]: 10 reviews were of critically low quality, 3 reviews were low quality, 44 reviews were moderate quality, and 14 reviews were high quality (See Supplementary Tables S4–S7: quality of studies).

The principal outcome was safety and efficacy in 50 SR and 13 SR dealt with issues concerning translation of the ATMP from animal to human subjects (translation T1) (Table 1). 13 SR were about therapies for osteoarticular pathologies, 14 SR for cardiovascular diseases and 9 SR for cancer (Table 1). The classification labelled "Other" includes

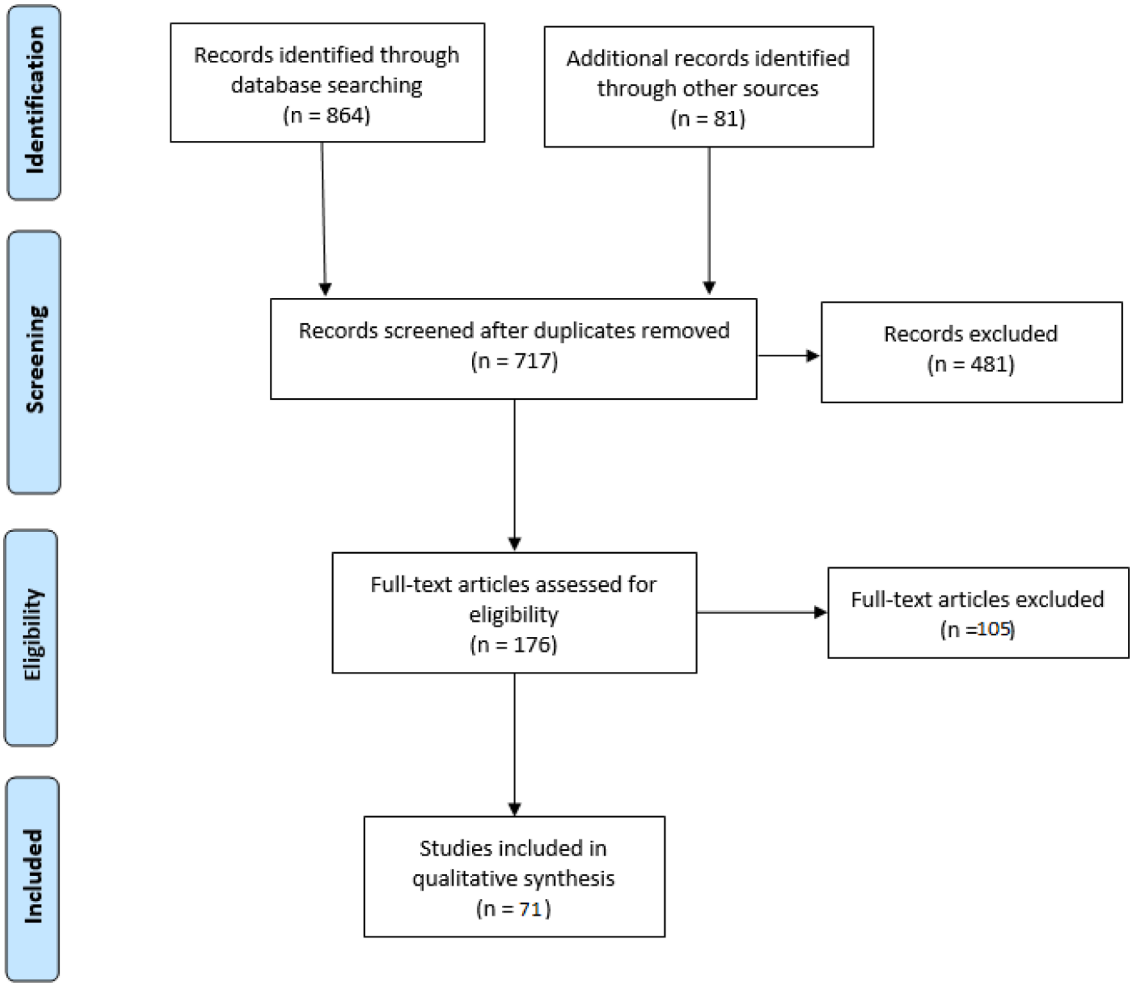

Fig. 2. PRISMA flow chart.

Table 1
Division of the included systematic reviews according to the type of main outcome and the type of pathology for which ATMP is indicated.

PathologyMainoutcome	Cardiovascular	Cancer	Osteoarticular	Nervous	Various	Other	Total
Safety and efficacy	11	8	11	6	1	13	50
Safety only	0	0	0	0	1	0	1
Economic	1	1	0	1	2	5	5
Translation T1 (*)	2	0	2	2	1	6	13
Translation T2 (†)	0	0	0	0	2	2	2
Total	14	9	13	9	3	22	71

Notes (*) refers to systematic reviews (SR) about the translation of ATMPs from pre-clinical studies to human subjects (†) refers to SR about the translation of ATMPs into clinical practice.

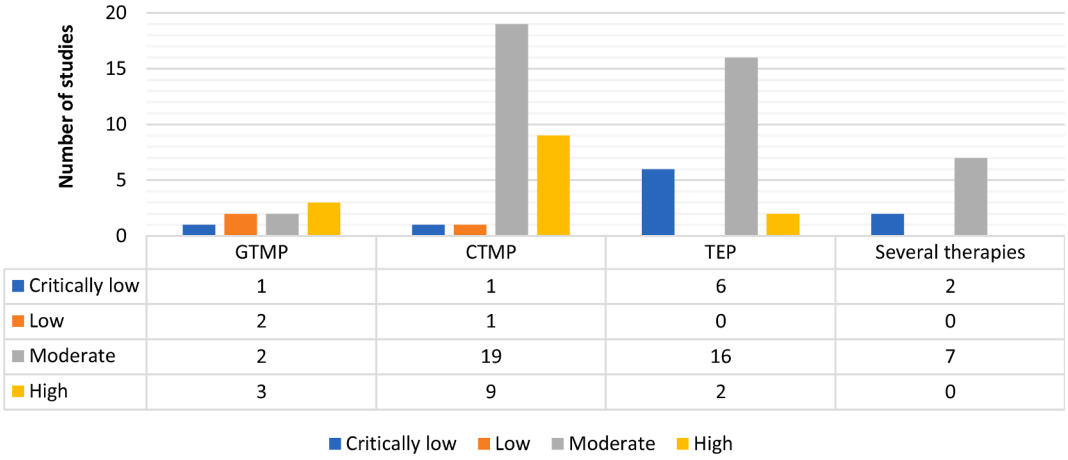

Fig. 3. Division of included full-text systematic reviews by quality and type of ATMP. Abbreviations: *GTMP* gene therapies medicinal products, *CTMP* cell therapies medicinal products, *TEP* tissue engineered products.

indications for diabetes, rare diseases, liver failure, aesthetic applications, dental interventions, burns, repair of tracheal defects or otorhinolaryngology.

Only a small number of included SR explicitly studied ATMPs with marketing authorization (Zolgensma, Yescarta and Kymriah) (See Supplementary Table S8: Summary of SR that evaluated efficacy and safety). The SR were often unclear about the source of human cells (patient or donor), or also included other sources. 35 of the SR reviewed evidence about only one therapy, while 2 reviewed more than 10 therapies. These may not exclusively be ATMPs, though we excluded SR where most therapies were not ATMPs. Over half of the SR included studies with multiple versions of a given ATMP (protocol modifications), due to different ATMP application protocols in the included clinical trials, which could lead to heterogeneities in the results obtained from those trials.

17 SR only included RCT, 28 SR included other types of clinical studies in human subjects (with or without RCTs) and the 26 SR included evidence from both pre-clinical (animal) and clinical (human) studies (See Supplementary Table S8). All the RCT studies used a comparator group, while less than half of the non-RCT reviews compared the efficacy of the intervention with a control group. 4 out of 17 SR that only included RCT did not find a single eligible study and hence provided no evidence. The SR of other types of clinical study included between 2 and 43 publications, while the systematic reviews that included pre-clinical studies included between 14 and 224 publications. 5 out of 50 SR that evaluated efficacy and safety found major added therapeutic benefit, 16 found moderate benefit, and 14 suggested minor benefit or promising based on current evidence (See Supplementary Table S9).

3.2. Barriers to evaluation and translation identified by the systematic review studies

The studies included in the systematic review were classified according to their outcome(s) and the barriers that the authors of these studies highlighted in these reviews for the evaluation and translation of ATMPs. The barriers were classified according to the domains established in the EUnetHTA Health Core Model 3.0 [28] (Table 2). The most frequently cited barriers were those that encompassed clinical effectiveness: insufficient number of studies to draw a conclusion (60/71) and the low quality of those studies (38/71), such as small cohorts, single-centre trials, single-arm trials and non-randomised studies. 9 SRs mentioned lack of follow-up about long-term effects. Another frequently cited barrier was around the technical characteristics of the technology: uncertainty about the mechanism of action and lack of standardization (36/71). Concerns or uncertainty about safety were cited in 18 SR. 14 SR cited concerns about the cost, budget impact or cost-effectiveness. Organisational aspects included translation T1 or T2 (23 studies), logistics, manufacturing or the viability of the business model. 6 SR mentioned misgivings about the patient perspective, and 6 cited regulation and legislation as a barrier.

4. Discussion

This review aims to add to the current literature by providing insight into the barriers identified by different stakeholders throughout the development cycle of ATMPs and their different applications. This objective is based on a comprehensive and methodological literature review that includes expert reviews from different stages in the development cycle. In addition, it attempts to detect all types of barriers and to analyse their implications, such as economic barriers, legislative barriers or evaluation barriers.

We chronologically organise the discussion section according to the phases of the product development cycle (Fig. 1). In the case of withdrawn therapies, we tried to identify the reasons for discontinuation from EMA documents and industry reports. However, the underlying cause is often disputed or unclear.

Table 2
Barriers to evaluation and translation of ATMP identified by the included systematic reviews.

EUnetHTA Health Core Model 3.0 Domain	Detected barriers	Number of included systematic reviews in which the barrier is detected
Number of studies	**Total number of studies included in the systematic review**	71
Technical characteristics of the technology	Uncertainty about mechanism of action	23
	Lack of standardization of the therapy	36
	Lack of databases of clinical and preclinical studies	2
Safety	Safety concerns or uncertainty	18
Clinical effectiveness	Not enough trials / studies	60
	Concerns about the quality of included trials	38
	Lack of understanding of long-term effects	9
Costs	Concerns about costs or cost-effectiveness	14
Organisational aspects	Uncertainty about translation T1 and T2	23
	Concerns about logistics and manufacturing	3
	Concerns about the business model	3
Patient-related aspects	Concerns about patient perspective	6
Legal aspects	Uncertainty about regulation and legislation	6

4.1. Translation from animal to human subjects

The first transition studied is the translation of the product from pre-clinical (animal) studies to human subjects, referred to here as translation T1. Our review has identified many therapies and indications that are considered "promising" by the authors although current evidence is weak. These might be candidates for further investigation and possibly, clinical trials. The review indicates several factors that might need to be considered at this point by developers and potential sponsors.

The manufacturing of ATMPs are especially complex so, in order to ensure a high-quality product, regulators pay particular attention to the supply chain and the shelf life of the product. For example, Provenge [9] (that needed to be infused intravenously over a period of approximately 60 min) and MACI [29] (for which the supply chain comprised two steps: (1) patient biopsy received at the manufacturing site to process the product, (2) product delivery to the administration site). Both ATMPs were finally withdrawn from use in the European Union. **Manufacturing decisions** made during the early stages of research and development can have long-lasting consequences for a project's subsequent commercial feasibility. On the one hand, finalising manufacturing processes early in the development process may be economically unattractive due to high failure rates at this stage of the process. On the other hand, making changes to manufacturing processes later in the product development pathway results in increased risks of development delays [30].

A related decision which might need to be early addressed is whether to employ cells from **autologous or allogeneic sources.** In some types of ATMPs either option might be feasible, and each has advantages and disadvantages [31]. Autologous cells can be easier to manipulate when dealing with a small number of patients and when the manufacturing site is close to the patient. Allogeneic cells can be associated with serious adverse events such as graft vs host disease and need to be preserved. These considerations can mean that autologous cells can be an attractive option during the early scientific development phase, but it can prove difficult to obtain functional cells from diseased patients and controlling quality and costs of manufacturing can be challenging if the therapy needs to be scaled up to a larger or more dispersed patient population. Four of the 6 withdrawn ATMPs used autologous material. MACI (an autologous cell therapy product) authorization expired in Europe because of the absence of an approved manufacturing site, though competition from HE alternatives also influenced the company's decision [10]. Some companies stated that they wish to withdraw from autologous products to re-focus on allogeneic [32]. The manufacturer of Provenge filed for bankruptcy in part because it could not service the financial costs incurred in scaling up manufacturing capacity to meet demand [28]. Strimvelis, an autologous gene therapy for a very rare condition, maintains control over the manufacture by restricting availability to one hospital in Milan. Scaling up can also be a challenge for allogeneic cell products, but centralized manufacturing centres can achieve economies of scale [30].

Just under half of the studies in this review drew attention to the lack of standardization among ATMPs under development, especially among studies that focus on the translation from preclinical to clinical. Goldberg [33] disfavorablynoted the high degree of **ad-hoc improvisation** among surgeons who are innovating in this area, and a lack of learning from successes and failures. Cousin [34] recommended an urgent need for **standardization of preclinical models**. The fast pace of development and frequent protocol modification also creates a subsequent evidentiary **challenge for regulators** [23], and creates an uncertain regulatory framework that is learning at the same pace as new developments take place [33].

Cousin [34] finds a high rate of failure to translate from the pre-clinical to clinical stage. The reasons included lack of a commercial partner, insufficient financial resources, a research group not involved in translation, and lack of expertise in regulatory affairs. Goldberg [33] notes a lack of **connectivity between the *in vitro*, pre-clinical and human data** and a "patchwork quilt of synergistic evidence". They did not find a single group that had carried out and reported studies in all three categories. Over one quarter of the studies in this review noted a need for fuller biological knowledge of mechanism of action. The failure of clinical investigators **to learn from the findings of pre-clinical studies** may be a factor in the modest clinical benefit demonstrated by some cell therapies [31] and the relatively high discontinuation rate of clinical studies [17]. Cousin [34] recommends closer collaboration between laboratory investigators, clinicians and the companies involved in commercialization. One suggestion for improvement is facilitating programs for the **education of future investigators** in the process of translation (T1 and T2) from discovery to improved health such as those funded by the National Institutes of Health Clinical and Translational Science Awards. Lam [35] proposes greater use of decision **support tools for translation from laboratory setting to clinical practice**. 2 of the 13 studies concerned with translation T1 identified the lack of databases as a barrier [36,37]. **Databases with shared resources** between researchers and clinicians should be promoted by public and private institutions, investing in their development and encouraging their use both at pre-clinical and clinical stages [38].

4.2. Regulatory approval

Regulatory approval requires evidence about effectiveness, safety and quality [3]. A minority of the SR highlighted concerns about the safety of the ATMPs under investigation. Most (apart from CAR-T) found that reported adverse events associated with the therapies were not severe and short-lasting.

Most of the authors of the reviews included in this study emphasise that further **high-quality clinical studies** are needed. According to the *Alliance for Regenerative Medicine* 152 ATMPs are currently in industry sponsored Phase III trials [7]. In 2020, Ronco et al. [6]. reported that of the clinical trials on ATMPs detected in the clinicaltrials.gov database, 37% were funded by pharmaceutical companies, 17% were co-funded

by public-private agreements and 46% by other resources. Given the large investment costs involved in setting up manufacturing facilities and generating clinical evidence [39], startups often do not aim to produce and sell drugs but license the intellectual property to large pharmaceutical companies or seek other forms of financial partnership [40]. Nevertheless, authors of systematic reviews downgrade studies that are funded by commercial sponsors for the risk of publication bias [41]. Clinical investigators need to be aware of, and to follow, recognised approaches to conciliate commercial funding with avoiding bias. For example, clinical studies need to be **registered and follow pre-published protocols** [42]. National and regional agencies can play a role in providing advice and **promoting public / private collaborations** and acknowledging the credibility of industry-funded studies that adhere to guidelines [42].

Many ATMPs are intended for patients whose needs are unmet by the current standard of care. In such cases, an RCT comparing the intervention to standard care might be considered unethical. Rare diseases are often, but not always, associated with unmet need. 14 of the 19 ATMPs approved by EMA had orphan designation [3]. Development of therapies for rare diseases can be challenging because of difficulty to recruit patients for clinical studies and the small potential market to obtain a commercial return on investment. To offset these disadvantages the EU offers early support and accelerated approval for unmet need via the PRIME scheme and 10 years marketing exclusivity that goes beyond patent protection for orphan drugs [14]. Currently, 50% of the ATMPs authorised for industrial manufacture have obtained their authorisation through PRIME designation [43]. However, EMA gives conditional MA in such cases, so that the company that markets the medicine will provide additional data on benefits and risks. Nevertheless, such evidential requirements impose delays and costs. The manufacturer of Glybera cited the burden of collecting **post marketing clinical data** as one of the factors that contributed to the withdrawal from the market [44]. However, many of the ATMPs under development analysed in this article are neither orphan medicines nor for patients without other therapeutic options. For such medicines, the usual evidential requirements (such as Phase 3 RCTs) for marketing approval and reimbursement should be applied by regulators and considered by manufacturers.

4.3. Health technology assessment (HTA)

After regulatory approval, the next challenge is to negotiate a price and obtain reimbursement from national health services and health insurance funds. The usual route is for the therapy to be evaluated by HTA agencies. The criteria will vary from country to country, but usually take account of effectiveness, safety, cost-effectiveness, and budget impact and possibly other factors such as acceptability by patients and clinicians and translation into clinical practice [45].

Evidentiary requirements for reimbursement in national health systems will often be different from the efficacy, safety and quality criteria demanded by regulatory agencies for marketing approval [43]. Although not all countries routinely evaluate cost-effectiveness, all national health systems require demonstrable evidence of added therapeutic value, especially if manufacturers are seeking a high price.

5 included SR were economic evaluations [22,46–49]. 2 were of CAR-T [46,47] therapies, one of stem cell therapy for neurological diseases [48], and one of the regeneration of the pulmonary valve in infants [49]. Lloyd – Williams [22] focused on methodological challenges of economic evaluation of ATMPs across several pathologies. They highlighted the paucity of trial data to inform economic analysis and the lack of long-term data on final endpoints (quality of life or survival) and costs. Any approach to estimate added therapeutic value in the absence of final endpoints must be based on a sustained, measurable correlation between the surrogate endpoint and survival or quality of life. Health economists use models to extrapolate the long-term impact for surrogate endpoints on survival [22]. This is critical for ATMP since surrogate endpoints often estimate a greater treatment effect than the benefit when measured in overall survival, and furthermore short-term outcomes do not always translate into longer benefits [47]. The lack of proof of added therapeutic benefit at HTA stage was one of the reasons behind the failure of orphan drugs Glybera and Zalmoxis to obtain reimbursement at the desired price by key health systems, notably Germany, and their subsequent withdrawal [50]. Therapies such as CAR-T have obtained provisional reimbursement pending further evidence collection, and by negotiating discounts and performance-based reimbursement agreements [6,51]. Petrou [46] notes that, over time, there may be over-use of these agents off-label and in unauthorized indications, presenting the risk of treatment decisions being made without an evidence-base, as well as a creeping incremental overall expenditure. It has been suggested that for payers, budget impact rather than cost-effectiveness may be the key criterion [46].

Manufacturers claim that the different criteria and methods used by HTA agencies are laborious and time-consuming [52]. There are initiatives to try to promote a common approach across some HTA tasks. An example is EuNetHTA, that undertook collaborative reviews across EU countries. The new EU regulation for HTA has among its main objectives the joint clinical assessment (JCA) for centrally authorised medicinal products. This new regulation will firstly target ATMPs, cancer medicines and orphan drugs. It emphasises the importance of a JCA that includes scientific, clinical and economic aspects, and coordination among institutions at different regulatory levels to ensure progressive translation with high quality, transparency and timeliness process [53]. One of the most effective tools to promote dialogue between manufacturers and regulators/HTA bodies has been the EMA-EUnetHTA Parallel Consultation process [43].

4.4. Translation into clinical practice

Once marketing approval and reimbursement status has been secured, the next challenge is to ensure that patients who meet the criteria can access the therapy. This phase has been termed translation T2. Our review included 2 papers that dealt with some of the challenges associated with this phase [19,23]. Hanna [23] reviewed mechanisms for financing breakthrough therapies. The conventional way of paying for medicines is per unit at the point of consumption. Alternative approaches can be classified as financial agreements (discounts, rebates, expenditure caps etc.) and outcome-based agreements.

While the aim of financial agreements is to limit the budget impact, the aim of health outcome-based agreements is also to ensure that further evidence about health outcomes associated with the therapy will become available, either at patient level or at aggregate level [6,51].

Novel payment mechanisms do not substitute for rigorous HTA evaluation. The fundamental principle is that expensive innovative therapies for specific patient groups displace health system resources that were being used to treat other pathologies. Hence, the innovative therapy can only be justified if its therapeutic benefit is greater than the health lost by the other patient group. For therapies which appear to demonstrate value for money, but with substantial uncertainty, a health outcome- based agreement can allow patient access while further evidence is being gathered while mitigating risk for the health system.

Nevertheless, such contracts have transaction costs, often falling on the public sector. Setting up information systems to collect these data can be expensive, time-consuming for hospital staff to complete, and the data need to be validated and analysed to trigger contract payments or rebates [54].

A multiplicity of different payment schemes for the same medicine at national or even regional level, each with specific features, as well as the post-marketing surveillance required by EMA, also impose cost, data duplication and complexity on manufacturers [54]. Hence, there may be a case for attempting to **align the design of payment schemes across jurisdictions.** EMA runs the DARWIN project [55] to strengthen **EU-wide real-world data** to support regulatory decisions and

potentially this could be extended to inform HTA and outcome-based reimbursement schemes [56].

Eder [19] reviewed the 32 therapies authorised under the hospital exemption (HE) regulation in the European Union states according to the European Regulation (EC) No 1394/2007. The HE principle allows European states to legally administer an ATMP without marketing authorisation granted by EMA in certain circumstances. This only applies in a hospital setting on a non-routine basis for an individual patient and when no centrally authorised treatment or clinical trial is available. While the scale and scope of HE in most countries seems appropriate [57], in some cases HE seems to be used for other purposes, e.g. in Germany as an informal springboard or incubator to facilitate R&D and innovation [10]. However, HE is not designed for this purpose and is not intended to become an easier pathway to achieve clinical routine. Unfair competition provided under HE in Germany has been cited as one of the reasons for the commercial failure in Europe of commercialised MACI and Chondrocelect [10,57]. In some (but not all) countries, evidentiary requirements for HE are less stringent, burdensome and costly than for products seeking regulatory approval [10].The correct use of the **HE pathway should be reviewed**, including the case for homogenisation across countries of the criteria for granting and supervising HE. This homogenisation would allow a level playing field for patient access to certain ATMPs and rule out any suspicion of unfair competition with industrially marketed ATMPs.

4.5. Strengths and limitations

This umbrella review has studied barriers for evaluation and translation of a challenging class of medical products across several pathologies and phases of development. The classification of a particular therapy as an ATMP is complex. For products that have not yet received marketing authorization we applied our judgement based on the description in the paper and the European regulation. The reasons for withdrawal of marketing authorization are not entirely clear from the official EMA website and we used reports from industry analysts and companies to complement these.

5. Conclusions and recommendations

This review has identified challenges and barriers for evaluation and translation of ATMPs across the product development cycle

The following recommendations for stakeholders and health policy makers arise from our review, and suggest the involvement of all stakeholders in the different stages of development and translation:

- National government should: Ensure markets are efficient in matching promising ATMP in development with appropriate public or private investors. Create an institutional and legislative framework that supports transparency and interconnectivity. Invest in infrastructure and institutions that facilitate data sharing.
- National health service payers and insure should: Set clear criteria for adopting the best therapeutic options for the benefit of patients given the resources available. Consider novel payment mechanisms after evaluation of effectiveness and efficiency. Align the design of payment schemes across jurisdictions.
- National HTA agencies should: Promote early dialogue with sponsors. Support joint clinical assessment. Ensure HTA methodologies are appropriate for ATMPs and current legislation.
- European and national regulators should: Ensure that regulatory evidentiary standards and post-marketing evidence generation plans align with the evidence requirements of HTA and payers. Promote early dialogue with sponsors.
- Manufacturers and commercial sponsors should: Seek early dialogue with regulators, HTA agencies and payers. Develop a plan for generating post-marketing evidence on effectiveness and safety. Undertake phase III randomised clinical trails that compare with standard care.
- Preclinical and clinical investigators should: Consider how early decisions about manufacturing, logistics and the source of cell material will scale up when implemented in clinical practice. Aim for standardisation of preclinical and clinical trials. Support use of shared databases to enable connectivity between *in-vitro*, preclinical and human studies. Learn about the process of translation from laboratory to practice and make use of decision support tools.

There are many challenges facing the translation of ATMPs from laboratory to patient, but some of these can be facilitated by a strong and clear health policy. According to our review, health policies should encourage contact between the different regulatory actors, assessors and developers of ATMPs, homogenise regulatory and HTA evidence criteria considering the specificities of ATMPs and promote economic collaboration initiatives.

Declaration of Competing Interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.healthpol.2022.10.007.

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