Molecular Therapy
Advances
Review

Designs of the clinical trials aiming at evaluating cell and gene therapy products: A critical appraisal from a literature review

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There is growing interest in advanced therapy medicinal products (ATMPs). However, there is debate about how they should be clinically evaluated. We aimed to assess the heterogeneity of trial designs used for ATMPs, based on a review of the most recently published ATMP trials from 2022 to 2024, and then make recommendations to improve the level of evidence. The 276 selected trials concerned CAR-T cells (28%), other gene therapies (22%), and somatic cell therapy (50%) and targeted different underlying diseases, hematological malignancies for CAR-T cells, genetic or congenital diseases for gene therapy, and other diseases for somatic cells ($p < 0.0001$). The most common designs were single-center (48%), early-phase (63%), single-dose (74%) designs; randomization was used in close to one-third of trials, more common in somatic cells (43%). The median sample size was the highest for CAR-T cells therapy trials (26 vs. 15 and 20 for other gene and somatic cells therapy, respectively), and the median follow-up was the highest for other gene therapy (23.5 vs. 15.4 for CAR-T cells and 12.2 months for somatic cells therapy). These results highlight the relatively short-term nature of evaluation of these innovative products.

INTRODUCTION

While Advanced Therapy Medicinal Products (ATMPs) are defined by the European regulatory framework as medicines based on genes, somatic cells, and tissues-engineered medicines for human use,[1] the US Food and Drug Administration (FDA) refers to these as cellular and gene therapy products,[2] and the Pharmaceuticals and Medical Devices Agency in Japan classifies them as regenerative medical products.[3] They can provide novel treatment alternatives to improve or even cure diseases that currently have no or inadequate standard-of-care options. These breakthrough therapies are thus growingly proposed in rare inherited genetic diseases, common immune diseases, cancers, as well as in regenerative medicine, that is, in a very large and heterogeneous set of patient conditions.[4] It may additionally concern orphan diseases, that is, high-risk or chronically debilitating diseases, which affect less than 5 in every 10,000 people, and usually miss satisfactory therapy. These ATMPs are expected to bring important health benefits, as exemplified by the development of autologous chimeric antigen receptor (CAR)-T cell therapies,[5] the first engineered cell therapy products to be approved by the FDA in 2017, and classified as a cell-based gene therapy for malignant hematological diseases including acute lymphoblastic leukemia, lymphoma, and multiple myeloma. The interests of such ATMPs have been recently also stressed out to address the challenges associated with organ and tissue transplantation.[6]

Currently, the evaluation of such new class of biologic products for human use has been integrated in the European Medical Agency (EMA) since 2007. Evaluations of decision-making for approval of gene and cell-based therapies[7] or tissue-based products[8] have focused primarily on the regulatory framework of the major health technology assessment (HTA) agencies, highlighting key differences in regulatory processes between the United States (US), the European Union (EU),[9] and Japan,[10] with more frequent use of nonconfirmatory evidence in Japan.[7,11] Previous reports have proposed several improvements for the current framework and established procedures for the regulation of ATMPs in Europe,[12] followed by national experiences and points of view, in Switzerland,[13] Germany,[14] and France,[15] among others. The EU has been dedicating resources toward ATMP development and its regulatory framework, via a recent dedicated research program funding, and a formal guidance currently in drafting from the EMA.[16]

For the last decade, many ATMPs have been extensively developed with many clinical trials ongoing over the world, as exemplified in 2016 by a review of international trial registries (ClinicalTrials.gov, the International Clinical Trials Registry Platform (ICTRP) of the World Health Organization (WHO), and EudraCT) that identified 939 clinical trials evaluating an ATMP between 1999 and June 2015, with increasing numbers over the years.[17] Subsequently, in 2023, 583 clinical trials evaluating 482 ATMPs were identified in

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the National Institute for Health and Care Research Innovation Observatory database, as of March 2022.[18] However, in the United States, there has been a significant use of FDA-mandated clinical holds on clinical trials, often related to adverse events.[19] Moreover, as of December 2024, six of the 27 ATMPs that have received marketing authorization in Europe since 2009 have been withdrawn and two not renewed in December, 2024, based on publicly available information.[20–22] Commercial reasons were invoked in all these cases of discontinued access in Europe, most often with high production costs combined with pricing negotiation issues across EU countries related to uncertain benefit-risk ratio. Of note, at least three of those withdrawn ATMPs in EU are still commercialized in the United States.

This called into question the conditions for assessment by the HTA bodies, which have developed a specific regulatory pathway for ATMPs,[23] in particular with regard to the level of clinical evidence. Indeed, clinical trials evaluating ATMPs should be approved according to a well-established regulatory process, including accelerated pathways, possibly on the basis of reduced information. Notably, in the review of international registries published in 2016, from the 939 clinical trials evaluating ATMPs, 47.2% targeted an enrollment of less than 25 patients, consistently with small-scale clinical trials and early clinical development schemes.[17] Such an early development phase was also evidenced in 2021, based on a review of 19 ATMPs approved in the EU, which reported mostly small, open-label, non-randomized, single-arm studies with historical controls and intermediate primary endpoints.[24] An update of this systematic review found 23 pivotal trials for 17 approved ATMPs in January 31st, 2021, 50% of which enrolled less than 76 patients.[25]

We hypothesized that the level of evidence of clinical trials conducted with ATMPs is heterogeneous and could be improved, either in terms of design, risk of bias, and reporting. A previous paper reviewed clinical trial designs, but only considered those used for approved products,[10] possibly resulting in a selection bias with respect to the general review objectives. So far, there has been no exhaustive review of ATMP trial publications to examine the methodological and statistical aspects of current practice in clinical evaluation of ATMPs.

Therefore, we aimed to evaluate the sources of heterogeneity in the trial designs used for ATMPs, regardless of the approval of the ATMP evaluated, to answer the question "How are ATMPs clinically evaluated"? We conducted a literature review of all recently published clinical trials evaluating ATMPs in the medical literature. Based on our observations, we propose some recommendations to improve the level of evidence and to answer another question: Could the level of uncertainty be reduced?

RESULTS

Figure 1 displays the study flow chart. Of the 374 articles retrieved from the PubMed search, 276 studies were selected.[26–301] They include 77 (28%) trials on CAR-T cells, 61 (22%) on other gene therapy including 47 *in vivo* gene therapy and 14 *ex vivo* stem cell gene therapy, and 138 (50%) on products based on somatic cells with the objective of repairing, replacing, or regenerating human tissue, subsequently referred to as "somatic cells" therapy.

Trial heterogeneity

The global setting of the trials differed between the three ATMP groups (Table 1). Industrial co-authorship increased from cell therapies (33%) to gene therapies (77%) ($p < 0.0001$). The type of ATMP product also varied by continent of first author's affiliation, with 56% of trials in Asia evaluating CAR-T cells, compared to 26% in the Americas, and 20% in Europe ($p < 0.0001$). The ATMP groups appeared clearly driven by clinical indications: CAR-T cells mostly targeted hematologic malignancies (78%), while other gene therapies mostly targeted genetic and congenital diseases (74%), and somatic cells were more heterogeneous in population (67%) ($p < 0.0001$) (Figure 2). Furthermore, although ATMPs trials had generally been conducted in adult patients, in more than 75% of publications regardless of the ATMP, other gene therapy trials exhibited slightly more frequently pediatric populations ($p = 0.0003$), possibly in line with genetic/congenital indications. In contrast, regardless of the ATMP, half of the trials (52%) were multicenter, of which more than a third were international.

Design heterogeneity

Otherwise, the design characteristics of the trials also differed between ATMPs (Table 2). First, in contrast with the early setting of the trials (about two-thirds of early-phase trials, regardless of the type of ATMP), efficacy was a primary reported objective in less than half of the CAR-T cells trials, compared with about two-thirds of somatic cells therapy trials and of other gene therapy trials ($p = 0.014$). Such distribution was mostly concordant with the registered primary outcomes in clinical registries as accessible at the time of review. Of the 224 publications that reported an NCT number, 161 (72%) publications were concordant with the registered outcome in terms of efficacy and/or tolerance and/or feasibility. Among the 160 trials that reported an efficacy outcome as primary in the publications, 129 had a registered outcome measure, including 45 (35%) not registered as an efficacy outcome on ClinicalTrials.gov; these findings did not depend on the type of ATMPs. Second, the most common design was a "single-dose" design, where the ATMP was administered similarly to all enrolled patients at a single-dose level, accounting for a decreasing proportion of trials across types of ATMPs, from 74% of somatic cell therapy trials using single-dose designs to 62% of CAR-T cells and 56% of other gene therapies ($p = 0.027$). In most cases, there was no comparison to a control group, although there was a comparison more often in somatic cell therapy trials than in CAR-T or gene therapy trials ($p = 0.0001$), which may be explained by the clinical context of therapies targeting orphan diseases or administered as a last resort at very advanced stages of diseases with no alternative treatment options; all of these comparisons were randomized, except for eight that used a comparison to external data, of which seven evaluated somatic cell therapy and one a gene therapy other

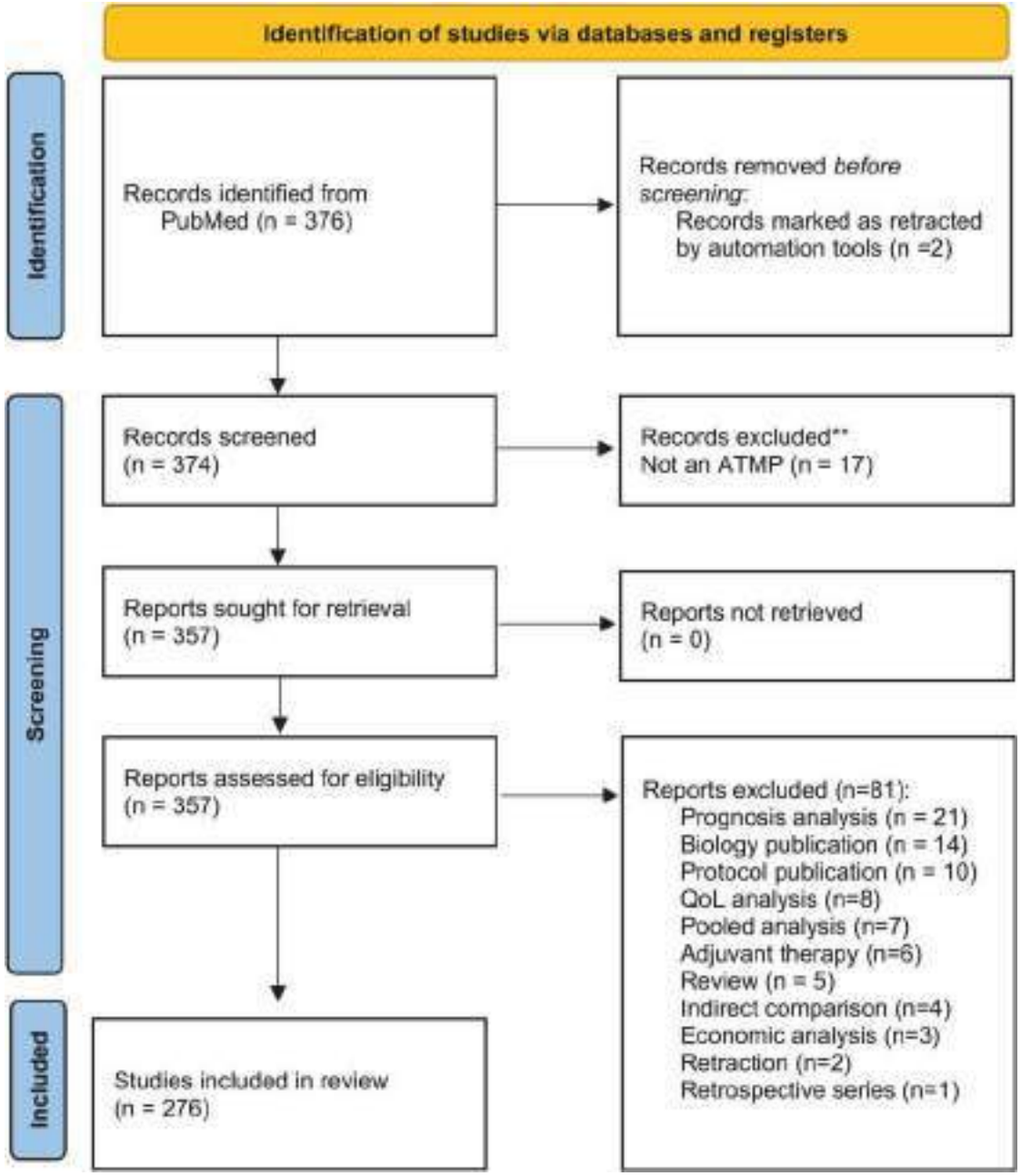

Figure 1. Study flow chart

than CAR-T cell. Third, when more than one dose level was used, differences in design between ATMPs were less pronounced: the most common study design was dose escalation (79%)—often a 3 + 3 scheme—although this was slightly less common in somatic cell therapy trials (75% vs. 83% for CAR-T cells and 82% for other gene trials) (p = 0.23). In contrast, heterogeneity in the statistical analysis of trial data across ATMP trials was low (Table 3). Regardless of the ATMP, most publications (78%) reported the primary analysis, without sample size calculation (77%). Although the actual median sample size varied between ATMP types, with medians ranging from 15 (other gene therapies) and 20 (somatic cells) to 26 for CAR-T cells (p = 0.003), it is likely to depend on the trial phase (Figure 2). Median follow-up was often missing, more so for somatic cells therapies (54%) than for CAR-T cells or other gene therapies (p < 0.0001); when reported, it ranged from 12.2 months in somatic cells therapy publications to 15.4 months in CAR-T cells and 23.5 months in other gene therapy trial publications (p = 0.079).

Table 1. Comparison of trial characteristics according to the type of cell and gene therapy product

Characteristics of the trials N (); median (IQR)	CAR-T cells therapy, *n* = 77	Other gene therapy, *n* = 61	Somatic cells therapy, *n* = 138	*P* value
Central registration	68 (88)	52 (85)	109 (79)	0.20
Time from registration and first inclusion, days: median (IQR)	16 (−2; 78)	13 (−35; 130)	7 (−82; 139)	0.51
Time from first inclusion to publication, months: median (IQR)	50.6 (37.7; 65.6)	69.5 (54.9; 88.7)	69.7 (44.5; 85.3)	0.0001
Publication				
Impact factor	20.1 (10.1; 58.7)	15.6 (6.7–68.1)	5.7 (3.6–9.7)	<0.0001
Industrial authors	48 (62)	47 (77)	45 (33)	<0.0001
First author's country of affiliation	–	–	–	<0.0001
Americas	31 (40)	34 (56)	55 (40)	–
Europe	14 (18)	21 (34)	32 (23)	–
Asia	31 (40)	6 (10)	34 (25)	–
Middle East	1 (1)	0	17 (12)	–
Population[a]				
Adults	70 (91)	48 (79)	126 (91)	0.040
Children/infants	10 (13)	21 (34)	15 (11)	0.0003
Pathology	–	–	–	<0.0001
Hematological malignancy	60 (78)	0 (0)	9 (6)	–
Solid tumor	10 (13)	8 (13)	30 (22)	–
Genetic/congenital	2 (3)	45 (74)	7 (5)	–
Miscellaneous	5 (6)	8 (13)	92 (67)	–
Enrollment	–	–	–	0.013
Single center	37 (48)	22 (36)	69 (50)	–
Multiple national sites	21 (27)	14 (23)	36 (26)	–
Multiple international sites	17 (22)	17 (28)	15 (11)	–
Unreported	2 (3)	8 (13)	18 (13)	–

IQR, interquartile range.
[a]More than one option was possible.

Single-dose vs. multiple-dose designs

Finally, in addition to the ATMP, we looked for differences that might explain the use of single-dose versus multiple-dose designs (Table 4). In short, the choice of the number of dose levels was related to the disease being studied, with 55% of solid cancer trials using mostly multiple-dose levels and 61% of hematologic malignancies trials preferring a single-dose level ($p < 0.0001$). Single-dose trials were more likely to use comparisons (including randomized comparisons) ($p < 0.0001$), to have larger sample sizes ($p = 0.001$) and to have longer follow-up times ($p = 0.020$) than multiple-dose trials.

DISCUSSION

There is a widespread expectation of clinical advance with the increasing numbers of ATMPs, including those emerging for the treatment and cure pediatric diseases.[302] Thus, several reviews of ATMP have been published, that mostly focused on development[17] or approvals[7] but more rarely on the results of clinical trials and the level of uncertainty regarding the clinical effect of ATMPs. In 2016, small sample size, single-arm trials, and adaptive designs have been reported to be used in registered clinical trials, likely due to complexity of the ATMP.[17] About a decade later, we aimed to assess the heterogeneity in clinical trial design and the level of uncertainty about the clinical effects of ATMPs, whether approved or not. To our knowledge, this is the first literature review that comprehensively examined current practice in clinical evaluation of ATMPs, regardless of regulatory approvals. We focused on cells and gene therapies, whereas many studies have only considered gene therapies.[303] This contrasts with our review, where somatic cells therapy eventually represented 50% of our sample. In addition to the evidence of heterogeneity, we aimed to provide some guidance on how to improve the level of evidence.

Firstly, there is a room for improvement in trial design. We confirmed our hypothesis of large heterogeneity and a low level of evidence in ATMP trials, with three main designs used roughly in

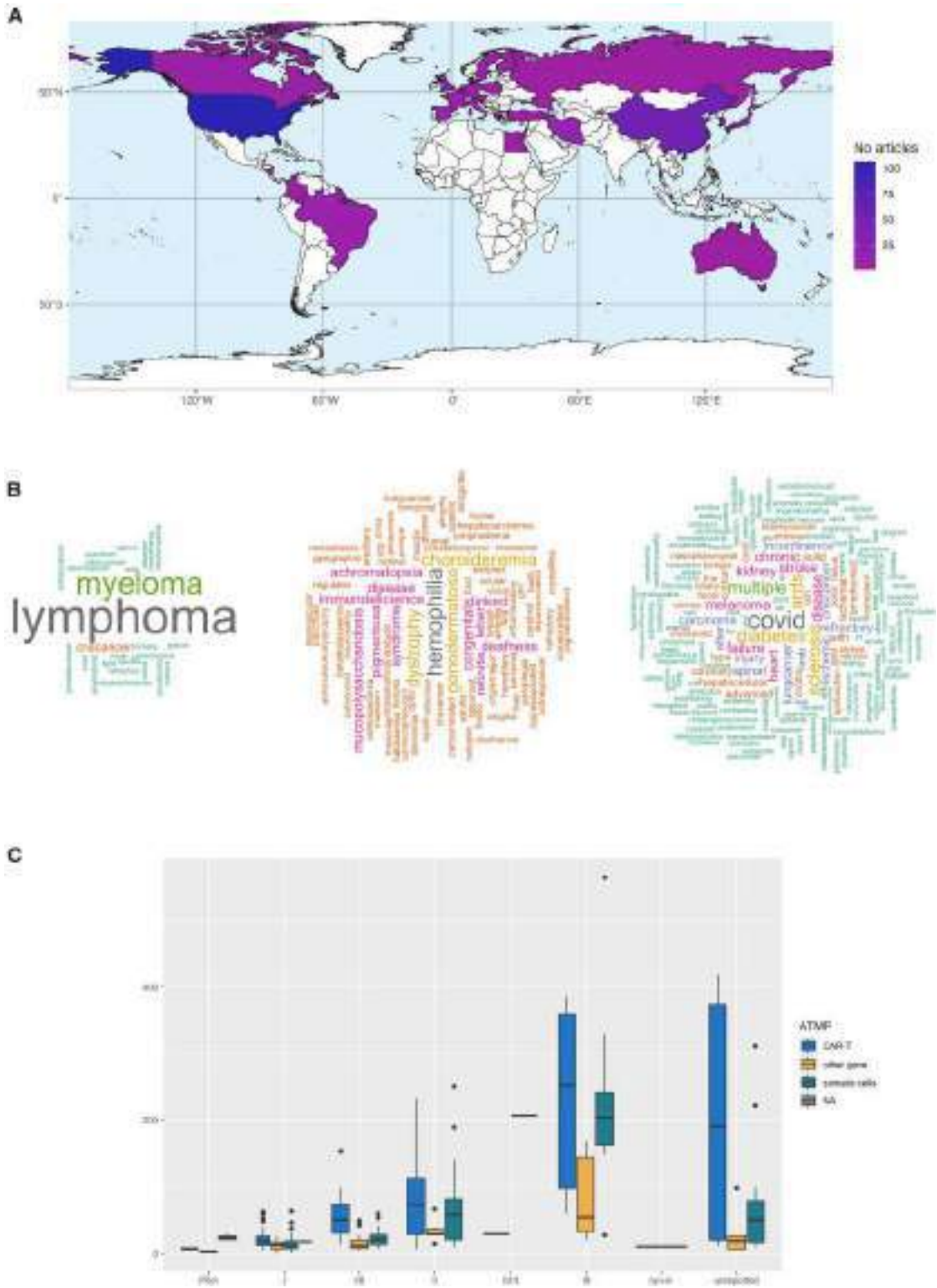

Figure 2. Features of included trials on advanced therapy medicinal products (ATMPs)

(A) World distribution of first authors' affiliation of the ATMPs articles. (B) Word-cloud of the enrolled diseases according to the type of ATMP, either CAR-T cells (left plot), other gene therapy (middle plot), or somatic cells therapy (right plot). (C) Boxplot of number of enrolled patients in the trial according to the ATMP type and trial phase.

Table 2. Comparison of designs according to the type of cell and gene therapy product

Characteristics of the trials N (%), median (IQR)	CAR-T cells therapy, *n* = 77	Other gene therapy, *n* = 61	Somatic cells therapy, *n* = 138	*p* value
Phase	–	–	–	0.13
Early*	51 (66)	39 (64)	84 (61)	–
Phase 2	13 (17)	6 (10)	28 (20)	–
Phase 2–3	0	2 (3)	1 (1)	–
Phase 3	8 (10)	9 (15)	8 (6)	–
Unreported	5 (7)	5 (8)	17 (12)	–
*Details				
Run-in	*0 (0)*	*0 (0)*	*1 (1))*	–
Pilot	*2 (3)*	*2 (3)*	*6 (4)*	–
Phase 1	*36 (47)*	*10 (16)*	*49 (35)*	–
Phase 1/2	*13 (17)*	*27 (44)*	*28 (20)*	–
Objective				
Tolerance	58 (75)	44 (72)	99 (27)	0.84
Efficacy	34 (44)	40 (66)	86 (62)	0.014
Feasibility	10 (13)	2 (3)	19 (14)	0.082
Registered main objective	*n* = 64	*n* = 56	*n* = 104	–
Tolerance	39 (61)	33 (59)	52 (50)	0.33
Efficacy	25 (39)	23 (41)	52 (50)	–
Similar to that reported in the publication	45 (70)	39 (70)	77 (74)	0.86
No of doses	1 (1;3)	(1;3)	1 (1;2)	0.020
Single dose	48 (62)	34 (56)	102 (74)	0.027
Several doses	29 (38)	27 (44)	36 (26)	–
Direct or indirect comparison	10 (18)	6 (21)	40 (51)	0.0001
Randomization	10 (13)	8 (13)	60 (43)	<0.0001
Multiple-dose designs	***n* = 29**	***n* = 27**	***n* = 36**	–
No of doses	3 (3;3)	3 (2;4)	3 (2;3)	0.54
Design	–	–	–	0.23
Dose escalation	24 (83)	22 (82)	27 (75)	–
Randomly allocated dose	0 (0)	3 (11)	5 (14)	–
Unreported	5 (17)	2 (7)	4 (11)	–
Single-dose designs	***n* = 48**	***n* = 34**	***n* = 102**	–
Design	–	–	–	<0.0001
Single dose, no comparison	38 (79)	28 (82)	36 (35)	–
Single dose, randomized comparison	10 (21)	5 (15)	55 (54)	–
Single dose, external comparison	0 (0)	1 (3)	7 (7)	–
Unreported	0 (0)	0 (0)	4 (4)	–

IQR, interquartile range.

equal proportions: one-third dose-escalation designs, one-third single-dose designs (32%), and one-third providing confirmatory evidence against either placebo or standard of care or other active therapy. It should be acknowledged that disease-indication-related constraints may explain some design characteristics in ATMP clinical trials. This was evidenced, for instance, in the case of other gene therapy publications, the majority of which focused on congenital/hereditary diseases. These studies had the smallest sample sizes, which is consistent with the fact that these are rare, or possibly ultra-rare, diseases. Similarly, the limited use of randomized controlled designs in ATMPs settings was consistent with previous reports of a 43% prevalence of phase 3, slightly above our findings, and 56% of the pivotal trials using single-arm designs.[25] In fact, because ATMP products often target rare or frail populations with poor

Table 3. Comparison of analyses according to the type of cell and gene therapy product

Characteristics of the trials N (%), median (IQR)	CAR-T cells therapy, *n* = 77	Other gene therapy, *n* = 61	Somatic cells therapy, *n* = 138	*p* value
Timing of analysis	–	–	–	0.049
Primary	60 (78)	40 (66)	115 (84)	–
Interim	7 (9)	11 (18)	8 (6)	–
Secondary	9 (1512	10 (16)	11 (8)	–
Subset	1 (1)	0	3 (2)	–
Sample size				
Sample size justification	20 (26)	8 (13)	34 (25)	0.23
Actual sample size	26 (13; 68)	15 (8.8; 29)	20 (10; 50.8)	0.003
Actual follow-up, months	15.4 (10.1; 19.1)	23.5 (12;36)	12.2 (6; 24)	0.079
Not reported	18 (23)	19 (31)	75 (54)	<0.0001
≥60 months	1 (2)	5 (12)	3 (5)	0.085

IQR, interquartile range.

prognosis, randomized trial designs may present difficulties in acceptance or ethical concerns. This likely depends on the rarity of the diseases under study, the severity, or the possible slow disease progression, all points that have been stressed out for a specific and individualized approach for clinical trials.[304] It should be noted that newly proposed adaptive designs, which may be imbalanced toward the most favored treatment arm, may provide acceptable alternatives while ensuring comparison with a randomized control group. Otherwise, it is important to remember that single-arm trials cannot avoid bias in assessing the effect of an intervention.[305,306] In fact, any causal interpretation of the treatment effect and its magnitude depends on external assumptions about patient outcomes in the absence of the investigational product. Indirect comparisons using natural history, registry, RWD, or prior study data can provide a comparative assessment of the treatment effect under different assumptions.[305] However, only 5 of 110 single-arm designs in our review sample were reported to include a formal external comparison to a reference group, potentially violating the underlying assumptions of group exchangeability.

Second, the need to report longer-term follow-up of these study data, based on the early stages of development of these products, should be emphasized. The actual short follow-up data of less than 24 months in 75% of the trials, with only five publications with a median follow-up of more than 5 years, should be substantiated by longer follow-up after the trial, as observed in registries or real-world data outside the trial.[307] In fact, it is expected that patients will be followed-up in subsequent extension studies or registries to comply with regulatory guidelines; this underscores the need to share and publish long-term follow-up data for advanced therapies.[308]

Trial reporting should also be improved, toward increased clinical trial transparency. Consistently with a previous study, which found that reports of trials from non-large companies were less transparent than those from large companies,[309] we found evidence of deficient reporting in ATMP trials, which are often driven by small scale companies or academic structure, except CAR-T cell trials. There were still 9% of publications with intractable central registration ID, and of those that were registered, 40% were registered after the trial has started. Nevertheless, there was no evident difference in time of enrollment after registration between the ATMP type ($p = 0.51$). In contrast, and as expected with regard to the sample size, time to publication after the first inclusion was increased in CAR-T cells trials compared to gene therapy and somatic cells ($p = 0.001$). This was also exemplified by sample size justification, which was reported in only 22% of trials, and the median follow-up, which was reported in only 59% of trials. Moreover, when central registration ID was reported in the publication, there were some discrepancies in the main outcome of the trial between publication and registration in about 25% of cases.

All these issues could easily be handled and transparency improved, following available generic clinical trial reporting guidelines that are applicable to designs used for ATMP trials,[310] including extensions for dose-finding designs[311] and adaptive designs[312] or use of external cohort or routinely collected data.[313] This is consistent with previous statements calling for improvement and strengthening of the level of evidence in the evaluation and reporting of trials of cell and gene therapy products.[314]

Finally, regarding less actionable sources of heterogeneity, we found differences in ATMPs across continents and countries. The observed differences in the type of ATMP product being evaluated between continents are consistent with previous studies that have reported differences in the approval of ATMPs between the United States, the European Union, and Japan.[7,11] This may raise concerns about the differences in regulatory jurisdiction, for example between trials conducted under the EMA and the FDA. Nevertheless, ATMP trials were mainly conducted in the North America regardless of the type

Table 4. Comparison of trial characteristics according to the number of assessed dose levels

Characteristics of the trials N (%); median (IQR)	Multiple-dose level $N = 93$	Single-dose level $N = 183$	p value
Publication			
Impact factor	10.4 (5.0; 31.6)	7.1 (3.7; 21.0)	0.053
Industrial authors	55 (60)	86 (47)	0.045
Population[a]			
Adults	82 (88)	161 (88)	0.96
Children/infants	14 (15)	32 (17)	0.61
Disease	–	–	<0.0001
Hematological malignancy	27 (29)	42 (23)	–
Solid tumor	27 (29)	22 (12)	–
Genetic/congenital	21 (23)	33 (18)	–
Miscellaneous	18 (19)	86 (47)	–
ATMP	–	–	0.030
CAR-T	29 (31)	48 (26)	–
Other gene therapy	27 (29)	34 (19)	–
Somatic cells therapy	36 (39)	101 (55)	–
Phase	–	–	<0.0001
Early[b]	85 (91)	89 (49)	–
II	4 (4)	43 (23)	–
II-III	1 (1)	2 (1)	–
III	1 (2)	24 (13)	–
Unspecified	2 (2)	25 (14)	–
Comparison	8 (9)	78 (43)	<0.0001
Randomized comparison	8 (9)	70 (38)	<0.0001
Sample size			
Sample size justification	8 (9)	54 (29)	0.0001
Actual sample size	16 (11; 26)	25.5 (10.8; 66)	0.001
Actual follow-up, months	12 (6; 22.2)	17.4 (12; 25.3)	0.020
Not reported	45 (48)	67 (37)	0.060
≥60 months	1 (2)	8 (7)	0.39

[a]More than one option was possible
[b]Run-in, pilot, phase 1 or 1/2

of ATMP ($p = 0.10$). Industry involvement also varied according to the type of ATMP, being more prevalent for gene therapies (CAR-T and others), possibility reflecting the different level of financial resources required, which may not be accessible for strictly academic development and manufacturing.[315] In addition, most academic sponsors rely on competitive grants with limited funds and short time frames; this situation is even more problematic in rare diseases, where products will not be commercially viable, and there is no economic incentive for industrial partners. This is a major constraint in the field.

We limited the analysis to only the two most recent years at the time of data extraction, and this is a major limitation of the study. Further work based on longer time periods should be more representative of the field, to include possibly the higher number of on-going studies. This was particularly evident in the long time elapsed between initiation of patient inclusion and publication in 2022–2023, with median times ranging from about 4 years (for CAR-T cells) to more than 5 years (for other gene therapies and somatic cells). Therefore, this points out the difficulty to provide contemporaneous evidence of ATMP clinical trials.

In addition, because we were primarily interested in trial design, we did not include the publications of case series in the scope of our study. Interestingly, as a gross indicator, using the same search equation without filtering on clinical trials, we found 165 ATMPs publications tagged as case series. This further supports toward the early stage of development of these ATMPs.

In summary, while the research on ATMPs is increasing, some guidelines for clinical trials to support evidence for their use are still lacking. Based on this review, it appears that trial designs vary widely according to the type of therapy (cells or gene) and the disease being studied (malignant or genetic) but not according to the population (adult or pediatric). Regardless of these differences, the non-negligible amount of unreported information in publications deserves attention and suggests that improvements in the trial conduct and reporting are still needed.

MATERIALS AND METHODS

We performed a literature search in PubMed using the following keywords: ("ATMP"[Title/Abstract] OR "cellular therapy"[Title/Abstract] OR "cell therapy"[Title/Abstract] OR "gene therapy"[Title/Abstract]) AND ((clinicaltrial[Filter]) AND (humans[Filter]) AND (english[Filter]) AND (2022:2024[pdat])). We chose the three most recent years (2022–2024) in order to provide evidence of the most recently published data in this area, and we focused on clinical trials using the dedicated PubMed filter.

Based on our search, we identified 276 relevant articles dated between January, 1, 2022 and November, 30, 2023, then actualized on July, 21, 2025 to incorporate publications up to December 31, 2024. All articles were reviewed by the three authors. The following data from each included article were recorded: (1) study basic information: journal, title, publication date, country of first author, industrial authorship, clinical trial registry ID (such as ClinicalTrials.gov or EUDRACT or Korean Clinical Research Information Service, for instance), registration date, and date of first patient; (2) diseases, target population in terms of age, and number of centers and countries; (3) ATMP and number of doses; (4) design characteristics, including dose-escalation designs for dose-finding, randomization for dose-ranging, or single-arm trials, with or without external comparison, main outcome measures reported in the publication and in the clinical trial registry, and sample size computation; and (5) summary of results, including number of enrolled and analyzed patients, and median follow-up time. Finally, we recorded the dates of central registration, first patient inclusion, and publication.

Statistical analysis

Summary statistics are reported as medians with interquartile ranges (IQRs) or percentages. Comparisons between groups of ATMPs or designs used exact Fisher tests or non-parametric Wilcoxon tests. All tests were two-sided, with p values of 0.05 or less indicating statistical significance, and no correction for multiplicity was made.

All analyses were performed on R v.4.5.1 (https://www.R-project.org/).

DATA AND CODE AVAILABILITY

Data are available from the authors upon request.

CONSORTIA

JOIN4ATMP (https://www.join4atmp.eu/), team leaders and deputy, by institution: Annette Künkele, Stefanie Grunwald, Alessandro Aiuti, Bjarne Kuno Møller, Lucie Biard, Sylvie Chevret, Reno Debets, Stephan Mielke, Johan van Eldere, Antonia Müller, Silvia Martin Lluesma, Lorena Consolino, Matt Bolz-Johnson, Stefano Benvenuti, Ulrich Blache, Piret Fischer, Carmen Sanges. Full list of affiliations in Supplemental Information Online file.

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AUTHOR CONTRIBUTIONS

L.B., V.L., and S.C. conceptualized, designed, extracted data from relevant studies, and assisted with the draft/approval of this manuscript. L.B. and S.C. carried out the systematic search. The JOIN4ATMP consortium assisted in conceptualizing the study and interpreting the results of the study and in the draft/approval of this manuscript.

DECLARATION OF INTERESTS

The authors declare no conflict of interest.

SUPPLEMENTAL INFORMATION

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