



Alliance *for*
**Regenerative
Medicine**

**CLINICAL TRIALS
IN EUROPE:
RECENT TRENDS IN
ATMP DEVELOPMENT**



The Alliance for Regenerative Medicine (ARM) is the preeminent global advocate for regenerative and advanced therapies.

ARM fosters research, development, investment, and commercialization of transformational treatments and cures for patients worldwide.

By leveraging the expertise of its membership, ARM empowers multiple stakeholders to promote legislative, regulatory, and public understanding of, and support for, this expanding field.

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Recent Trends in ATMP Development

Background

Europe has been a pioneer in the field of advanced therapy medicinal products (ATMPs) and was the first region to adopt specific regulation for the development and approval of this new class of medicines. To date, the European Medicines Agency has granted the highest number of marketing authorisations with ATMPs worldwide and many of the ATMPs currently approved or in development originate from research centres in Europe. The quality of clinical research, with highly qualified centres and healthcare professionals across Europe, is also well recognised internationally. However, previous work has shown that there are some shortcomings in European Clinical Trial Directive 2001/20/EC, particularly for trials carried out in multiple Member States, and that this was associated with a decline in the number of clinical trials in the European Union.¹ In view of the sharp increase in the number of ATMPs in development during the last few years, the Alliance for Regenerative Medicine (ARM) wanted to characterise the attractiveness of Europe, including national disparities, for the clinical development of ATMPs, and any trends over time compared to other regions.

Objective

This analysis aims to identify recent trends in clinical trials with ATMPs in Europe, comparing and contrasting the number, type of technology, phase of development, or approval process for new clinical trials to other regions in the world and among different countries in Europe.

Methodology

Two approaches have been used for this analysis:

1. A global analysis of active, interventional clinical trials with ATMPs initiated during the January 2014 - June 2019 time period was carried out using available regulatory databases.* Given that many clinical trials are carried out in more than one country, the analysis by region was made counting each trial uniquely, with a separate category for multi-regional clinical trials, whilst the analysis by country was made counting clinical trials in every country separately.
2. An online survey with questions about clinical trials in Europe was carried out among ARM members during the first half of 2019.

Findings

Finding 1: Global analysis of all new clinical trials with ATMPs initiated since January 2014

As illustrated on page 2:

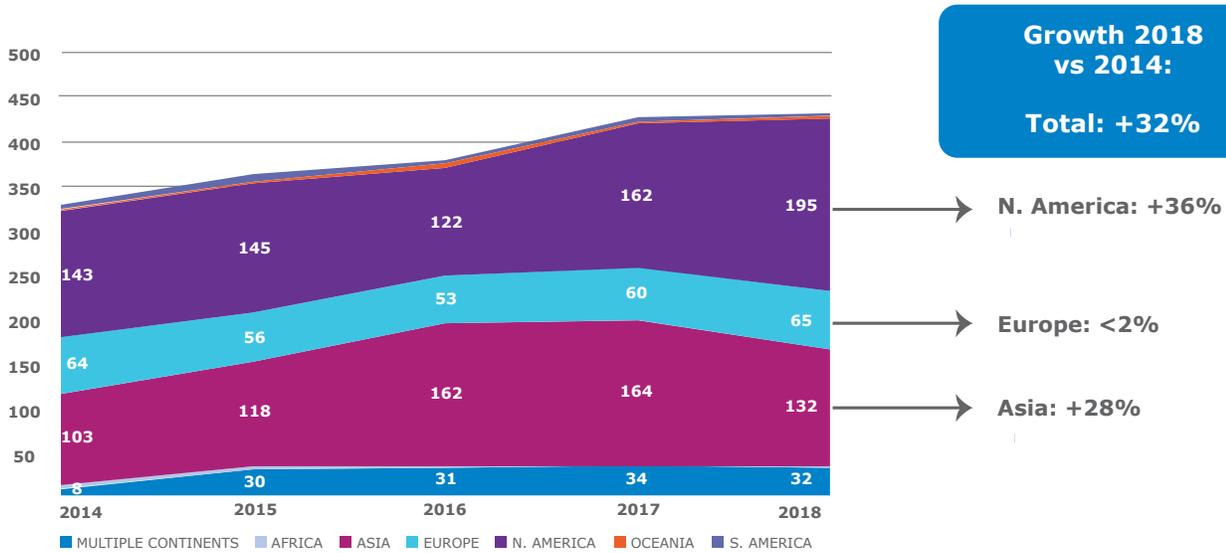
- › Three times as many new interventional clinical trials were initiated in North America than in Europe: A total of 2,097 new clinical trials were initiated between January 2014 and June 2019. The large majority of these new clinical trials were located in North America (845) and Asia (736), followed by Europe (323), South America (26), Oceania (17), and Africa (11). There were also 139 multi-regional clinical trials, with the majority involving countries in Europe (131) and North America (122).

* The following databases were used:

- U.S. clinicaltrials.gov
- European clinicaltrialsregister.eu
- Japanese - University Hospital Medical Information Network Center (UMIN-CTR) <http://www.umin.ac.jp/ctr/>
- Japanese - Japan Medical Association Center for Clinical Trials www.jmacct.med.or.jp/en/
- Japanese - the Japan Pharmaceutical Information Center (JAPIC) <https://www.clinicaltrials.jp/cti-user/trial>
- Current trials from the Australian/New Zealand, Chinese, S. Korean & Indian regulatory databases.
- Only active, interventional phase I-III with Regenerative Medicine/Advanced Therapies were included

- On a global scale, the number of new clinical trials with ATMPs increased by 32% during the 2014-2018 period. There was an overall marked increase in North America (+36%) and Asia (+28%), but not in Europe (<2%).

Clinical Trials Initiated 1 Jan 2014 – 30 June 2019, by Continent and Year

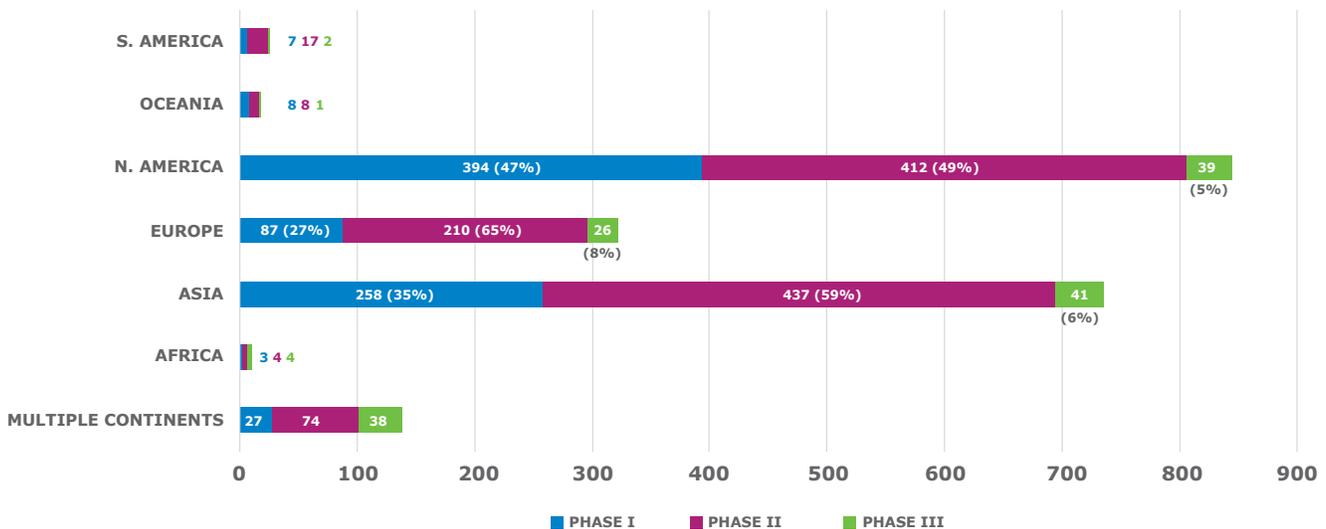


Total new trials initiated during the 2014-2018 period = 2,097

(All new trials initiated in more than one continent are included in the Multiple Continents category)

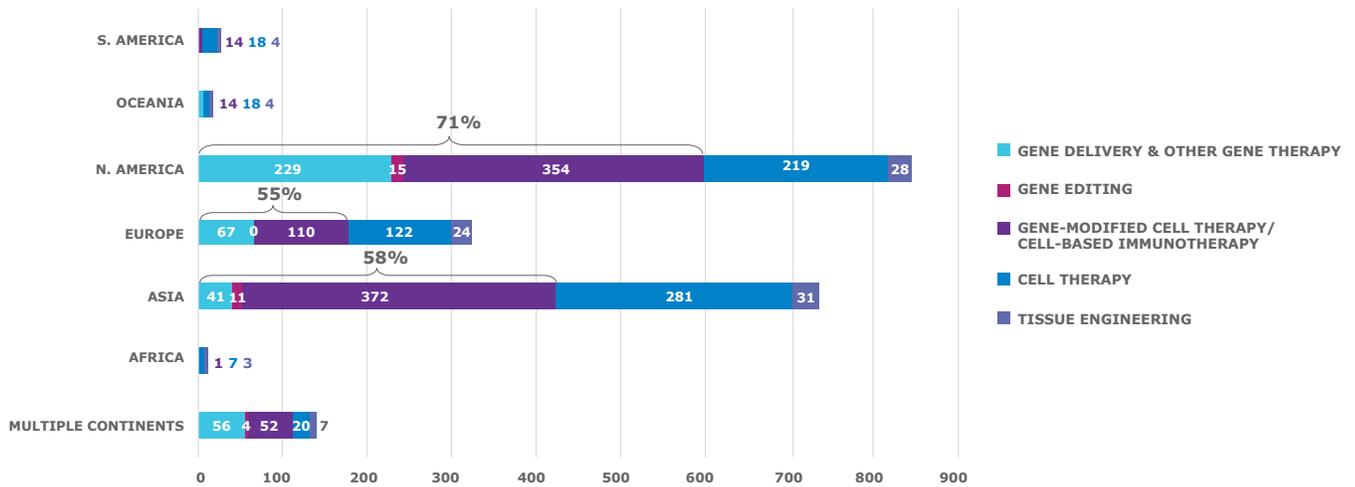
- There were proportionally more new Phase I trials reported in North America (47% of all new trials) than in Europe (27% of all new trials).

Clinical Trials Initiated 1 Jan 2014 – 30 June 2019, by Continent and Study Phase



- There were proportionally more new gene therapy clinical trials (utilising gene delivery, gene editing, and gene-modified cell therapy technologies) in North America (71% of all new trials) than in Europe (55% of all new trials).

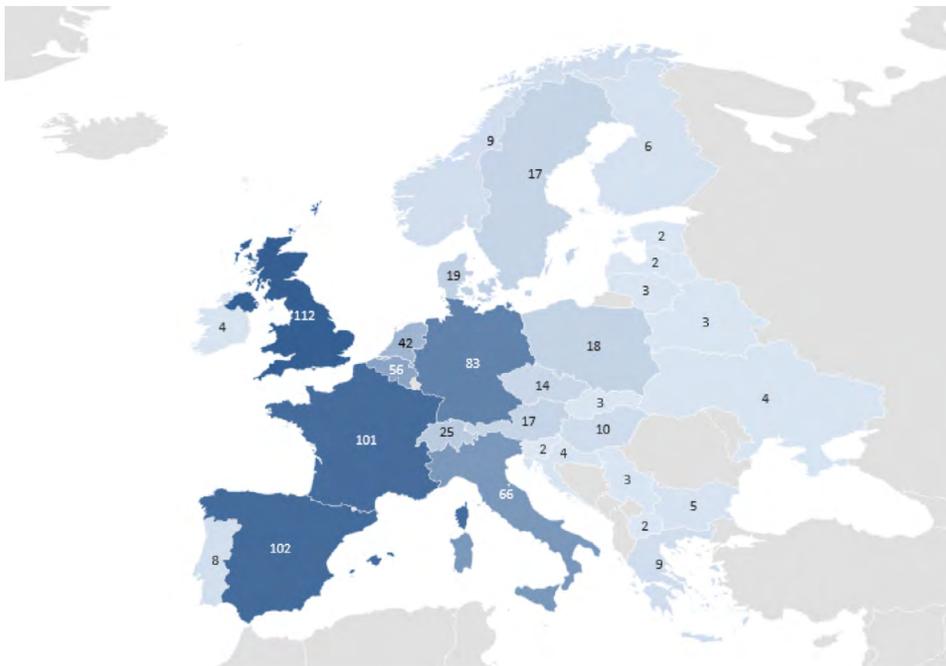
Clinical Trials Initiated 1 Jan 2014 - 30 June 2019, by Technology and Continent



Gene-modified cell therapies/cell-based immunotherapies represent 43% of all new clinical trials, followed by cell therapies (32%), gene delivery and other gene therapies (19%), tissue engineered products (5%), and products using gene editing (1,4%)

- In Europe, over the period 1 January 2014 - 30 June 2019, the UK (112), Spain (102), and France (101) initiated the highest number of new ATMP clinical trials, followed by Germany (83) and Italy (66).

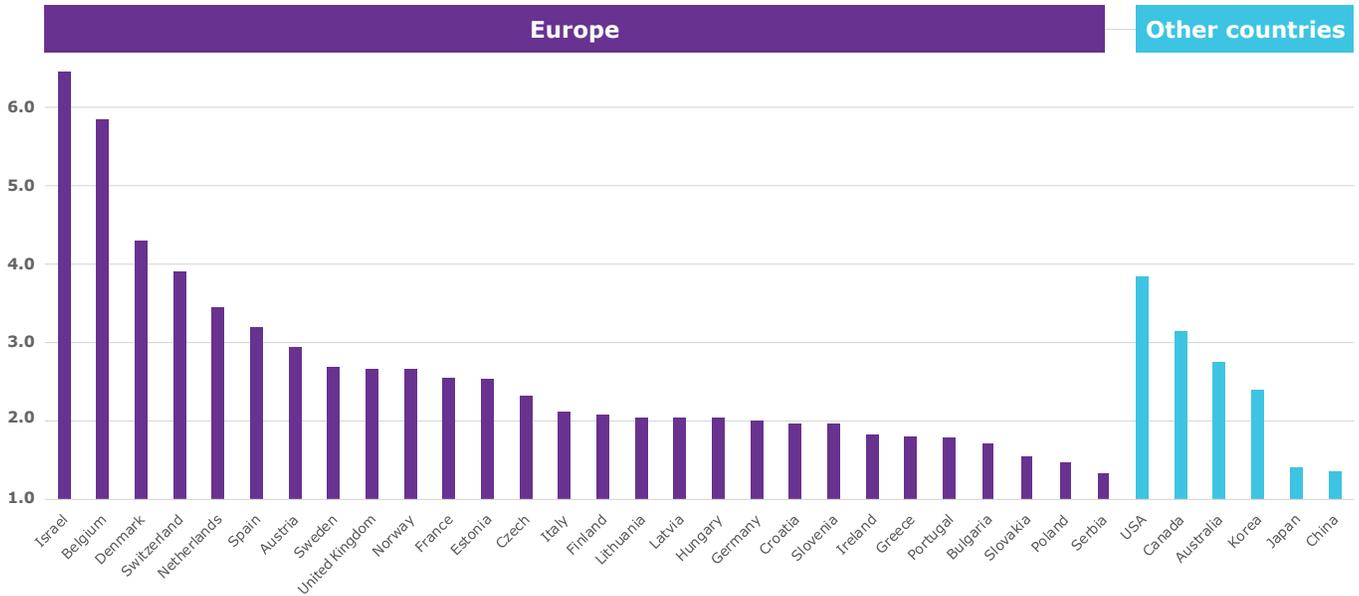
Clinical Trials Initiated 1 Jan 2014 – 30 June 2019, by Country – Europe



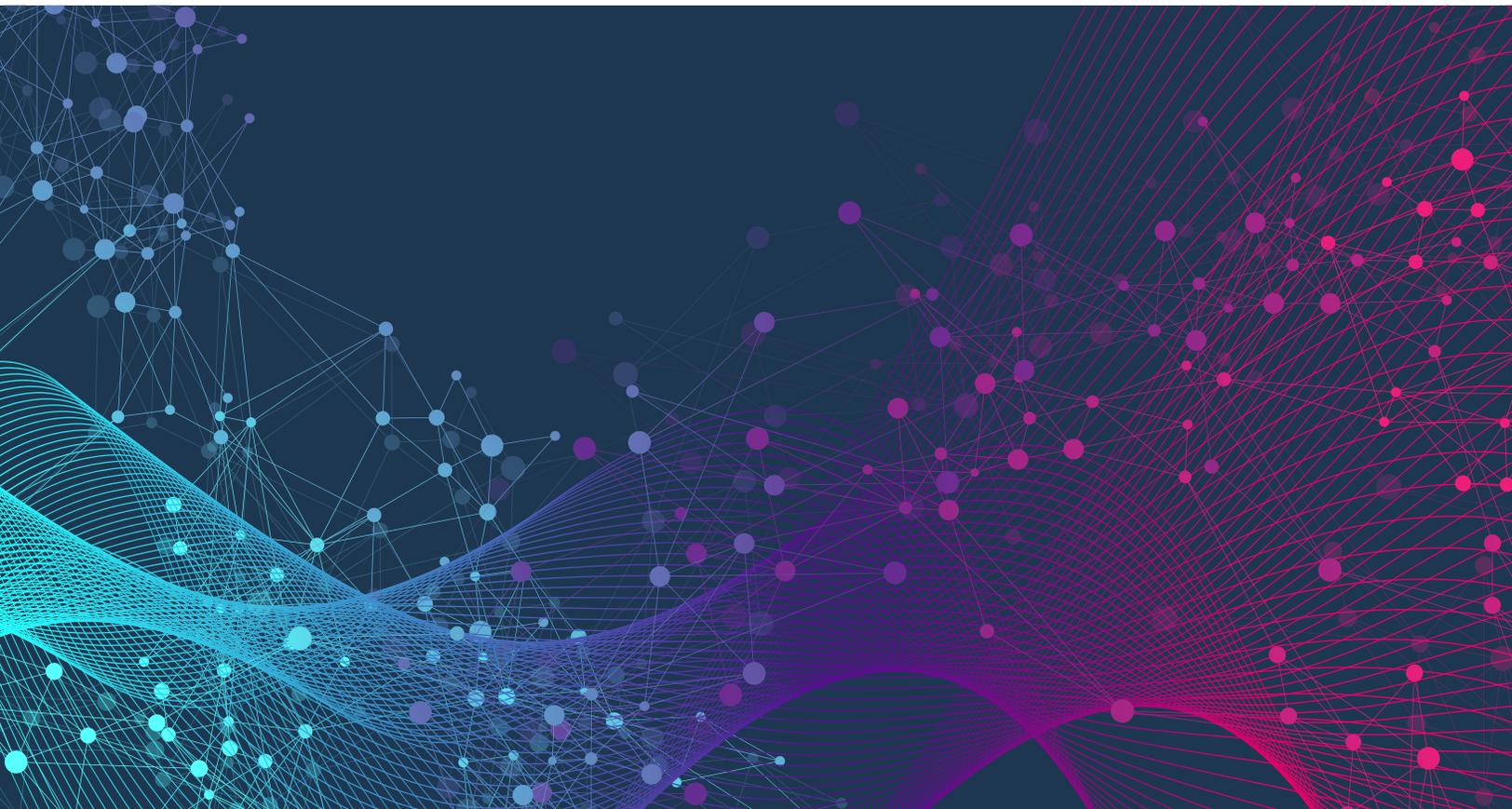
Note: Multinational clinical trials have been counted as separate trials in each of the participating countries (total Europe = 800)

- When the number of new clinical trials by country is examined relative to their size, there is a large variability among different European countries: Belgium, Denmark, and Switzerland attract proportionally more new ATMP clinical trials *per capita* than other countries, including the USA and Canada. Israel has the highest number of new ATMP clinical trials *per capita* in the world.

Clinical Trials Initiated 1 January 2014 – 30 June 2019, by Country, Per One Million Inhabitants



Note: Multinational clinical trials have been counted as separate trials in each of the participating countries



Finding 2: ARM Member Survey on clinical trials in Europe

- > A total of 22 respondents participated in the survey, 16 of whom represent organisations sponsoring clinical trials in Europe. Data were gathered on 30 ATMP clinical trials in Europe, 19 of which are multinational.
- > An overview of the number of clinical trials, their locations, the type of product being investigated, and the development stage is provided below.

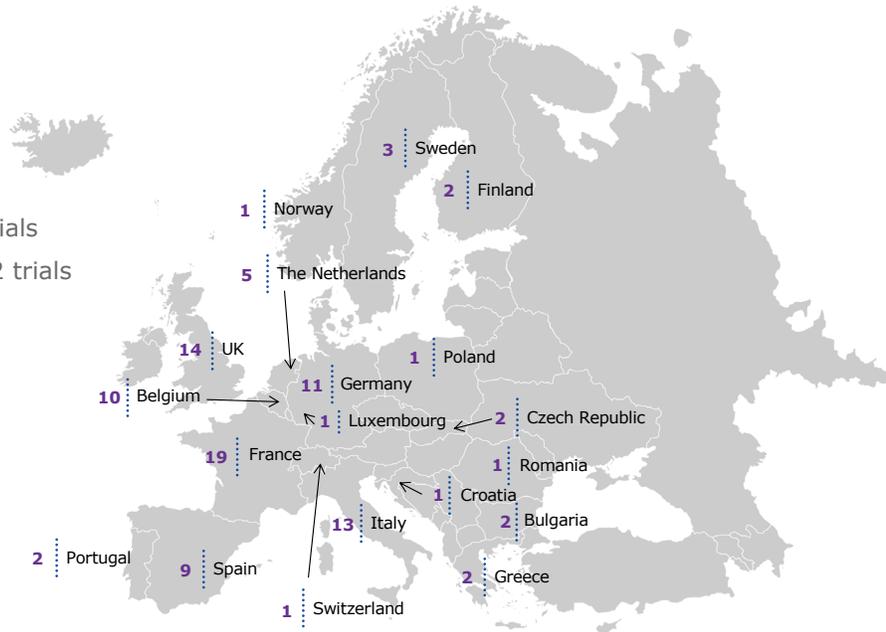
**30 TRIALS
IN TOTAL**
INCLUDING 19
MULTINATIONAL TRIALS

By product type:

Tissue-Engineered Product: 7 trials
Somatic Cell Therapy Product: 2 trials
Gene Therapy Product: 16 trials
Chimeric Antigen Receptor
T Cell Therapy: 5 trials

By phase:

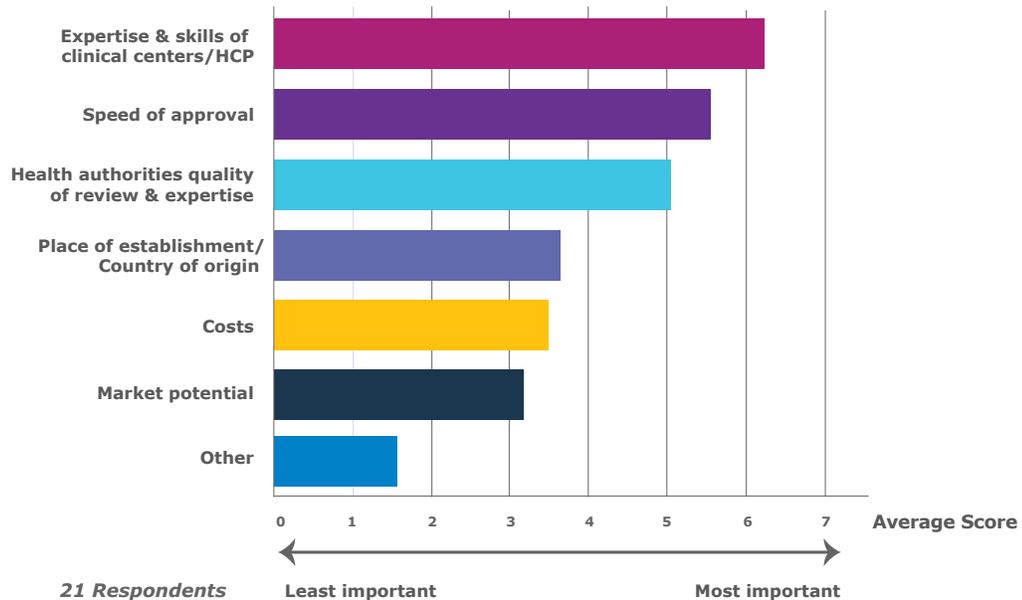
Phase I : 3
Phase I/II: 9
Phase II : 9
Phase II/III : 1
Phase III : 8



- > According to respondents, the most important criterion for selecting a clinical trial site and a country is the expertise and the skills of the clinical centers and healthcare professionals, followed by the speed of approval by regulatory authorities, and the quality of the review or expertise of the regulatory authorities.

Main Criteria to Select a Clinical Trial Site/Country

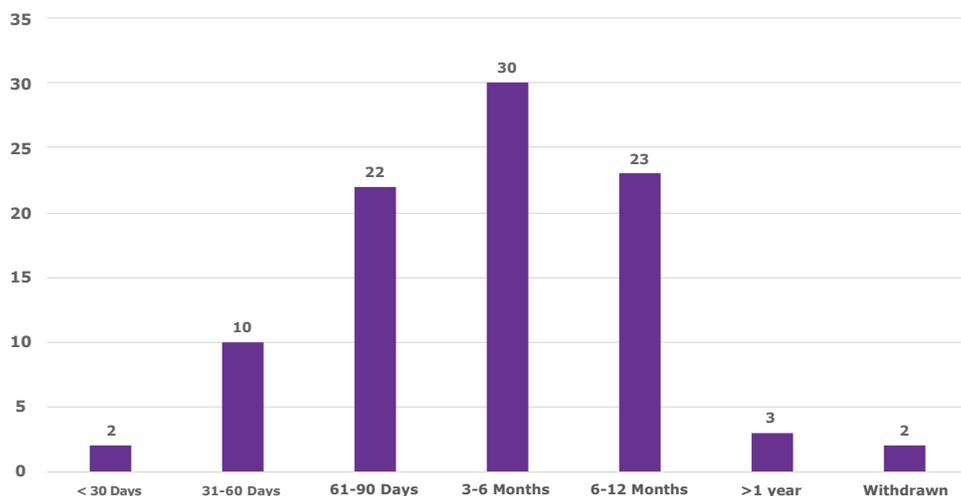
Answered: 21 Skipped: 1



- › Clinical trial authorisations are granted on a country-by-country basis after review by the national Ministry of Health or Health Agency, Ethics Committee, and, when relevant, authorities responsible for Genetically Modified Organisms (GMO). Based on the survey results, approval times for a new clinical trial in Europe vary from fewer than 30 days to more than a year, with an average approval time of three to six months.

Approval Times for Clinical Trials – All European Countries

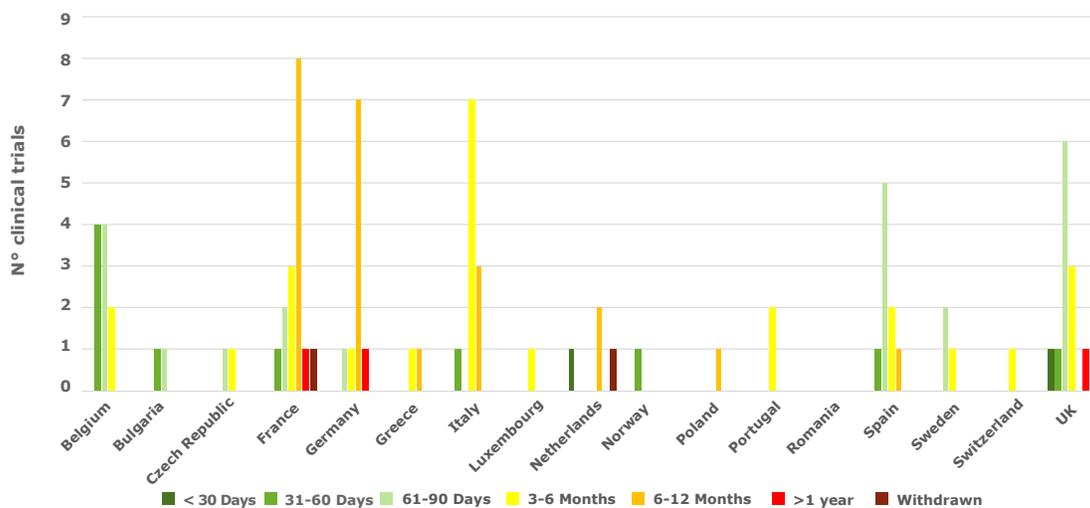
(26 ATMP clinical trials, of which 18 are multinational trials)



- › There is a significant country-by-country variation, as indicated in the chart below. The majority of clinical trials are approved six to 12 months after application in France or Germany, whilst approval was obtained within 60 days for the majority of clinical trials in Belgium and the UK. The number of questions raised by regulatory authorities before approval is also higher in France and Germany.

Approval Times by Country – Overview

N = 26 ATMP Clinical Trials, of which 18 multinational trials



- › Factors that increase the speed of approval and reduce the number of questions raised by regulatory authorities include conducting the national scientific advice procedure prior to the clinical trial application and the granting of a previous clinical trial approval for the same product in the same country.
- › Timelines for clinical trials with gene therapies are longer due to delays for approval of GMO aspects, which usually fall under the responsibility of the national environmental or agriculture authorities rather than health authorities. Respondents have indicated that GMO approval is particularly long in the Netherlands and has been a cause for withdrawal of a clinical trial application in that country.
- › Finally, a total of 214 amendments have been filed for 27 clinical trials in the survey. In about 10% of these cases, delays in the approval of a clinical trial amendment have contributed to delay or a suspension in patient recruitment. Based on the survey responses, this appears to occur more frequently in France.

KEY FINDINGS

- › Though the number of ATMP therapeutic developers based in Europe is approximately half of that based in North America, the number of clinical trials that have been initiated in Europe is only about a third of that in North America.
- › Whilst the number of new ATMP clinical trials has significantly grown over a 4-year period (+32%) on a global scale, with notable growth in North America and Asia, this trend is not present in Europe, where the number of new clinical trials remained consistent over the time period analysed.
- › The number of new gene therapy clinical trials is also proportionally lower in Europe (55% of all new clinical trials) than in North America (71% of all new clinical trials) but not significantly different from Asia (58%). There is considerable country-by-country variability in the number of clinical trials, speed of assessment, and time for approval of clinical trials in the different countries analysed in Europe.
- › In Europe, the UK, Spain, and France attracted the highest absolute number of ATMP clinical trials during the period analysed (112, 102, and 101, respectively).
- › Some smaller countries are, relative to their size, outperforming: Belgium, Denmark, and Switzerland attract proportionally more new ATMP clinical trials *per capita* than other countries, including in other regions such as the USA or Canada. Israel has the highest number of new ATMP clinical trials *per capita* in the world.
- › ARM members, via the survey, indicated the most important criteria for selecting a clinical trial site and a country is the expertise and the skills of the clinical centers and healthcare professionals, followed by the speed of approval, the quality of review, and the expertise of regulatory authorities.

Discussion

The fragmentation of regulatory bodies and ethical committees and the lack of harmonisation on various aspects (e.g. donor testing requirements, patient information consent forms, contracting agreements) across the different countries may contribute to a less attractive environment for clinical trials in Europe; however, other factors, such as the lower levels of investment and risk capital available in Europe, may also play a role.

The Clinical Trial Directive 2001/20/EC allows a delay of maximum 90 days for the review of clinical trial applications for ATMPs, with a possible extension by a further 90 days. This is longer than for other types of medicinal products, which require a decision within 60 days. Despite the longer timeline allowed for the review of ATMP clinical trials, the results of the ARM member survey indicate that decisions from regulatory bodies are often delayed.

Previous research has indicated that the time necessary to start a clinical trial, the harmonisation of the approval processes, and greater visibility of transnational network of centres of excellence can positively affect pharmaceutical clinical research and may bring significantly more clinical trials in Europe.^{1,2} ARM member survey results are consistent with these findings.

The analysis shows that some countries are, relative to their size, particularly successful attracting new ATMP clinical trials: Belgium, Denmark, and Switzerland are, relative to their size, outperforming other countries such as the USA or Canada in the number of clinical trials *per capita*. Belgium and Denmark have implemented policies and developed best practices that make them more attractive places for clinical trials, indicating that with political support, it is possible to act at national level and become more competitive.^{3,4} Examples of initiatives implemented in these two countries include a 15-day approval time for Phase I trials in Belgium and the implementation of a Clinical Trials Office and the creation of disease-specific networks in Denmark.

The lower number of gene therapy clinical trials in Europe compared to North America could be due to the classification of these therapies as GMOs, requiring specific approval by GMO authorities in Europe, a step that adds complexity to the clinical trial authorisation process, often extending the time necessary for approval.

Recommendations

Notwithstanding the quality of its clinical research centers, Europe could increase its attractiveness as a region for the development of ATMPs by improving timelines for approval of clinical trials in some countries and streamlining approval of multinational trials.

Improving and accelerating the process to approve gene therapy-based clinical trials, including consistent approaches for GMO review among different countries, is critical to ensuring these requirements do not create a barrier to initiating trials in Europe.

The Clinical Trial Regulation (EU) N° 536/2014, which is expected to be implemented by the end of 2020, is aimed at facilitating clinical trials across the European Union by streamlining the application procedure via a single entry point and harmonising the procedure for assessment of clinical trial applications. The implementation of the Clinical Trial Regulation is a unique opportunity to increase Europe's attractiveness for the conduct of ATMP clinical trials. However, the Regulation does not improve timelines for approval of clinical trial applications with ATMPs, which remain longer than for other types of medicinal products: the time between the application and the decision is maximum 110 days, with a possible extension to a maximum of 141 days if additional information is required.

It is important to ensure that ATMP clinical trials are approved in the shortest possible timeframes. To effect this, national competent authorities must allocate sufficient resources and ensure an adequate level of expertise for the review of clinical trial applications for ATMPs.

The interplay between the Clinical Trial Regulation with other applicable legislations such as the GMO Directives 2001/18/EC and 2009/41/EC, as well as the new Regulation (EU) 2017/745 for Medical Devices and Regulation (EU) 2017/746 for In Vitro Diagnostics will be of paramount importance to ensure that these do not act as disincentives to conduct clinical trials with ATMPs in Europe. As GMO and medical device approvals lie outside the Clinical Trial Regulation, ensuring timely and streamlined approvals will be necessary.

Conclusions

Previous work has shown that the European Clinical Trial Directive 2001/20/EC presented some shortcomings, particularly for trials carried out in multiple Member States, and was responsible for a decline in the number of clinical trials in the European Union. In view of the sharp increase of the number of ATMPs in development during the last few years, this report characterizes the attractiveness of Europe, including national disparities, for the clinical development of ATMPs, and trends over time compared to other regions.

The implementation of the above recommendations will contribute to maintaining a strong innovation base and important R&D investments in Europe, but, most importantly, this will be critical to ensure that European patients with serious diseases and only few or no alternatives can access these new transformative therapies at an early stage through participation to clinical trials.



"The European advanced therapy space is rich in expertise and innovation, with some individual countries outperforming the U.S. in terms of *per capita* participation in clinical trials. This research shows that improving the speed of approval and streamlining requirements for European multinational trials with ATMPs are critical to attracting more clinical trials in Europe. Our hope is that regulators and governments across Europe will see the need to reduce barriers while continuing to ensure patient safety and maintaining its level of excellence for clinical research."

— Janet Lambert, Chief Executive Officer, Alliance for Regenerative Medicine



"Time is an important driver when choosing a clinical trial location. In the USA, Investigational New Drug (IND) applications and subsequent protocols are reviewed by the FDA within a maximum of 30 days. The longer approval times and their related uncertainty make the conduct of multinational clinical trials in Europe more challenging than in some other regions."

— Anne-Virginie Eggimann, Senior Vice President, Regulatory Science, bluebird bio



"Europe has been at the forefront of innovation with ATMPs as the sector has matured and it is encouraging to see that there are so many potentially life-changing studies taking place across the continent. However, the number of clinical trials with ATMPs is variable from one country to another and we see that countries with shorter approval times, such as the UK, Belgium, Denmark, or Switzerland, attract more clinical trials. It is important to learn from these countries and replicate their performance across Europe. We remain excited by the prospects for the sector in Europe but to maintain its attractiveness and scientific leadership, we support the recommendations of ARM outlined in this report."

— Jacqueline Barry, Chief Clinical Officer, UK Cell and Gene Therapy Catapult



"Beyond the well-documented regulatory complexities, risk capital is limited and fragmented in Europe compared to the USA. This is a significant issue for European-based SMEs, as they often lack adequate resources for the clinical development of their product. This may be a contributing factor to the lower growth in the number of ATMP clinical trials in Europe, particularly later stage clinical trials, compared to other regions."

— Michael Hunt, Chief Financial Officer, ReNeuron



"The complexity for gaining the approval of multinational clinical trials with ATMPs is very high; there are commonly divergent national opinions from regulatory authorities on data requirements and between GMO authorities on GMO classification. The clinical trial regulation represents a unique opportunity to streamline the process, including for products at the interface with other legislations such as GMO-products or drug-device combinations. We therefore urge regulatory authorities to ensure that all aspects specifically relevant to ATMPs are looked at and addressed in an efficient and pragmatic way by the time the regulation is implemented."

— Jill Morrell, Director, Regulatory Research & Intelligence and EU Policy, BioMarin



"Europe has traditionally been at the forefront of innovation in advanced therapies, with many products originating from research in Europe. The number, network, and expertise of clinical centres are excellent, too. However, this research indicates that carrying out clinical trials in Europe is more complex and lengthy than in other regions. Improving the regulatory environment for clinical development is critical to ensure European-based ATMP developers are not in a competitive disadvantage compared to companies based in the US or elsewhere."

— Miguel Forte, Chief Executive Officer, Zelluna Immunotherapy

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Contact: Annie Hubert, Senior Director,
European Public Policy, ahubert@alliancerm.org

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