Cell and Gene Therapy Catapult
ATMP clinical trials report
2020
1. Executive summary

The number of advanced therapy medicinal product\(^1\) (ATMP) clinical trials in the UK continues to increase year-on-year, with 154 trials reported as ongoing in 2020, indicating more than a 20% increase from last year. This is representative of approximately 12% of all ATMP trials in progress globally\(^2\), which remains consistent with the 12% seen in the 2019 analysis, demonstrating the UK’s continuing global appeal as a destination for clinical development of ATMPs.

The majority (70%) of ATMP trials are investigating viral vector mediated gene therapies, with an even distribution between \textit{in vivo} and \textit{ex vivo} gene delivery method. Adeno associated virus (AAV) and lentiviral vectors are the most common \textit{in vivo} and \textit{ex vivo} gene delivery vectors, respectively.

Over the course of 2020, there was an increase in the number of ongoing UK ATMP clinical trials across all phases, except for Phase II/III trials which remained unchanged. We observed the highest increase in Phase II trials which grew by 42%, followed by a 27% increase in Phase III trials, a 20% increase in Phase I/II trials, and a 19% increase in Phase I trials. We are also reporting an additional Phase IV clinical trial.

It is important to note that throughout 2020 COVID-19 has greatly impacted the routine operations of society, business, and healthcare. As the MHRA does not need to be notified of interruptions to trials due to COVID-19, the true impact of the pandemic on all stages of clinical trials may not be yet fully ascertained and is likely to become more apparent in clinical activities over the next two to three years. Fewer trials were completed in 2020 compared to 2019, and whether this is a symptom of the pandemic delaying trial activities, or is due to more trials including longer follow-up periods is yet to be determined. However, with similar numbers of trials initiated in 2019 and 2020, despite the pandemic, this suggests that there is continued interest in conducting clinical trials for ATMPs in the UK.

The ongoing activities of the Advanced Therapy Treatment Centres network, funded by the UK government Industrial Strategy Challenge Fund, continues to support the development of the UK infrastructure for clinical adoption of these therapies. This network has been successful in building systems within the NHS to ensure that products progress effectively through clinical development and can be commercialised in the UK to reach patients.

\(^1\) As defined by EC ATMP regulation 1394/2007
To allow direct data comparison, only ongoing interventional trials in Phases I – III are included in the calculation for global percentage.
1.1 Introduction to the 2020 ATMP clinical trials database

The UK 2020 ATMP clinical trials database covers advanced therapy medicinal product (ATMP) clinical trial activities that the CGT Catapult understands to be ongoing in the UK as of December 2020. It supersedes the 2019 database and both are available at catapult.org.uk/clinical-trials-database.

The 2020 database has been compiled and verified by the CGT Catapult team, and includes:

- all ATMP trials, including non-interventional long-term follow-up (LTFU) trials
- academic and commercial trials
- ongoing trials in the UK, regardless of the nationality of the sponsor

For 2020, some re-categorization of data has been done due to increased transparency of key dates and milestones for ATMP clinical trials. From 2019 onwards, “new trials” now refers to trials initiated in the respective year. The trend data now shows the last five-year trends rather than from the start of the database in 2013.

1.2 The purpose of the CGT Catapult UK ATMP clinical trials database

The Cell and Gene Therapy Catapult was established as an independent centre of excellence to advance the growth of the UK cell and gene therapy industry, by bridging the gap between scientific research and full-scale commercialisation. With more than 330 employees focusing on cell and gene therapy technologies, it works with partners in academia and industry, NHS and Government to ensure these life-changing therapies can be developed for use in health services throughout the world. It offers leading-edge capability, technology and innovation to enable companies to take products into clinical trials and provide clinical, process development, manufacturing, regulatory, health economics and market access expertise. Its aim is to make the UK the most compelling and logical choice for UK and international partners to develop and commercialise these advanced therapies.

The UK ATMP clinical trials database aims to assess the progress and state of play of the UK ATMP clinical development landscape. The database is updated annually and provides, what we believe to be, a comprehensive and accurate review of the UK ATMP clinical trial landscape. The input of the cell and gene therapy community is important however to help us maintain its relevance, and we welcome updates, additions and corrections, which can be sent to us at clinicaldatabase@ct.catapult.org.uk.
2. Commentary on key findings 2020

2.1 The UK’s portfolio of ATMP clinical trials continues to grow

The 2020 UK ATMP clinical trials database shows the continued year-on-year increase of ongoing ATMP clinical trials. There were 154 trials ongoing in the UK in 2020, compared to the 127 trials reported in 2019. This has been part of a continuing trend of sector year-on-year growth. As shown in green below in Figure 1, there has also been a similar number of trials initiated during 2019 and 2020.

Figure 1: Number of ongoing, initiated, completed, and closed trials 2015-2020

*From 2019, trials shown in green are trials initiated during that year. For 2015-2018, the designation ‘new’ includes both trials registered and initiated each year.
2.2 Oncology remains the largest therapeutic area

The division of therapeutic indications among the ongoing ATMP trials remains largely unchanged from previous years. Oncology, which includes haematological malignancies and solid tumours, remains the dominant therapeutic area accounting for 35% of ATMP clinical trials, followed by haematology and ophthalmology (12% each), Figure 2.

Figure 2: Distribution of UK ATMP clinical trials by therapeutic area in 2020

“Other” therapeutic areas, together representing approximately 3% of UK ATMP clinical trials, includes dermatological, infectious disease, oral, and renal/urogenital clinical trials.

2.3 Trials initiated in 2020

In addition to being the largest therapeutic area investigated overall, oncology remained the largest therapeutic area of trials initiated in 2020, accounting for 28% of the clinical trials initiated this year. Haematology was the second largest therapeutic area targeted by trials initiated in 2020 (21%). This was closely followed by trials with therapies targeting metabolic diseases (18%), which has emerged as an area of greater interest, overtaking ophthalmology, which accounted for 9% of the UK ATMP clinical trials initiated in 2020 (data not shown). This reflects a significant increase in the overall metabolic trials observed from 2019 to 2020.
2.4 T cells are the dominant cell type investigated

The cell types investigated in ATMP clinical trials remain largely unchanged from 2019. T cells continue to be the dominant cell type, accounting for 44% of UK ATMP clinical trials, **Figure 3**. This is as expected since research into oncology, the largest therapeutic area, is largely T cell focused, and is consistent with previous years.

**Figure 3: Breakdown of ongoing UK ATMP clinical trials in 2020 by cell type**

![Figure 3: Breakdown of ongoing UK ATMP clinical trials in 2020 by cell type](image-url)
2.5 Majority of therapies in the database are genetically modified

Gene therapy trials currently account for 70% of the ATMP clinical trials in the UK, somatic-cell therapies account for approximately 20% of trials, whilst tissue engineered therapies make up the remaining 10%, Figure 4. Of the gene therapy trials, there is a fairly even split between *ex vivo* (53%), which includes CAR-T and transduced haematopoietic stem cell derived products, and *in vivo* (47%) genetic modification. These gene therapy trials are further discussed in the **Gene delivery technologies** section.

Figure 4: Breakdown of UK ATMP clinical trials in 2020 by ATMP type
2.6 Breakdown of UK ATMP clinical trials by Phase

The majority of the UK ATMP clinical trials observed in 2020 are in Phase I/II (39%), followed by Phase III (23%), and Phase II (18%), Figure 5A. The distribution by phases, broken down into gene therapy, somatic cell, and tissue engineering trials, is further shown in Figures 5B-D.

Figure 5A-D: Breakdown of UK ATMP clinical trials in 2020 by trial Phase

A. ATMP trials by Phase for 2020

B. Gene therapy

C. Somatic cell therapy

D. Tissue engineered therapy

N/A: A single Long-Term Follow-Up clinical trial has no Phase assigned. All instances of N/A in this report refer to this clinical trial.
2.7 Breakdown of 2020 UK ATMP trials by status

Overall, the majority of UK ATMP clinical trials are currently recruiting (53%) or in follow-up (26%), Figure 6A. All therapy types generally follow the same distribution, Figures 6B-D, however the proportion of trials in recruitment for somatic-cell therapies is significantly higher than for gene therapies and tissue engineered therapies. This suggests that the somatic cell therapy space is not as mature as the gene therapy space.

Although the largest proportion of tissue engineered trials are recruiting (41%), Figure 6D, this is notably lower than the overall number of trials recruiting. It is worth noting that tissue engineered therapies comprise only 10% of the ATMP therapies observed, therefore the actual number of trials is relatively low resulting in large percentage changes.

Figure 6A-D: Distribution of UK ATMP clinical trials in 2020 by trial status and therapy type

A. Distribution of UK ATMP clinical trials

B. Gene therapy

C. Somatic-cell therapy

D. Tissue engineered therapy
2.8 Distribution of 2020 UK ATMP trials by Phase and status

Of the total UK ATMP clinical trials recruiting in 2020, the majority (40) are Phase I/II, followed by Phase II (20), and Phase III (17), Figure 7A. As therapies develop, later phase clinical trials will begin to appear and, in 2020, we observed two Phase IV clinical trials recruiting.

Figure 7A: Distribution of 2020 UK ATMP clinical trials by trial Phase and status
Looking at the trials initiated in 2020, most of those are also currently recruiting, suggesting that trials continue to progress efficiently through set-up to active recruitment. The majority of these new and recruiting trials are Phase II or Phase I/II (six and five trials, respectively), Figure 7B. A late stage Phase IV trial, which was reported in the 2019 database, was initiated in 2020. The one suspended trial in Phase II that was initiated in 2020 was suspended due to the COVID-19 pandemic, and is now due to start in 2021, Figure 7B. As the MHRA does not require notifications of interruptions to trials due to COVID-19, there may be additional trials in a state of holding/suspension for which the status is not shown.

Figure 7B: Distribution of trials initiated in 2020 by trial Phase and status
2.9 AAV and lentiviral vectors are the predominant gene therapy technologies

The majority of gene therapy trials use either AAV vectors (39%) or lentiviral vectors (37%), Figure 8A.

For *in vivo* gene therapy clinical trials, we note that AAV based vectors remain the main vector of choice (81%) with a small proportion of trials using adenovirus (5%), lentivirus (4%), or non-viral vectors (5%), Figure 8B. For *ex vivo* clinical trials, the use of lentiviral vector delivery dominates (68%), followed by retroviral vectors (22%), Figure 8C. In 2020, we also see an emergence of non-viral *ex vivo* based gene therapies, which accounted for 5% of ATMP trials observed.

**Figures 8A-C: Distribution of gene transfer vectors in 2020**

A. Distribution of gene transfer vectors used in 2020 ATMP clinical trials

B. Distribution of *in vivo* gene transfer vectors used in 2020 ATMP clinical trials

C. Distribution of *ex vivo* gene transfer vectors used in 2020 ATMP clinical trials
The *ex vivo* vectors are predominantly used for CAR-T based therapies (CAR-T and CAR-T + gene editing) which account for 47% of *ex vivo* clinical trials. This is followed by “Gene corrections/insertion” therapies which account for 42%, Figure 8D. The *ex vivo* CAR-T and TCR based clinical trials almost exclusively focus on oncology, whilst gene corrections focus on multiple disease types (not shown).

**Figure 8D. Distribution of type of *ex vivo* gene therapy in ongoing clinical studies**
2.10 Long-term follow-up studies

Of the 22 long-term follow-up (LTFU) studies reported, 17 are currently recruiting, whilst three are in follow-up, and two have completed (not shown). Ophthalmology (27%) and oncology (27%) are the largest therapeutic areas, followed by haematology (14%), and metabolic diseases (14%), Figure 9A. Together, these account for over 80% of LTFU clinical trials. The majority of these LTFU studies are either Phase I/II, or Phase III trials, Figure 9B. Approximately two thirds of LTFU studies have an interventional aspect, the remainder being observational, Figure 9C.

The LTFU trials discussed in this section are distinct trials classified as LTFU, however there also continues to be ATMP clinical trials which include LTFU as part of their study design.

Figure 9A-D: Distribution of long-term follow-up studies by therapeutic area (A), trial phase (B), and intervention type (C).
2.11 Therapies continue to move into later Phase trials

There has been an increase in the number of clinical trials across all trial Phases, apart from Phase II/III trials which remained unchanged from 2019, Figure 10. The growth seen in 2020 of Phase III and IV trials is indicative of the ATMP space maturing and sponsors progressing though their clinical development programmes, with the approaching long-term safety studies. Additionally, many new umbrella trials have started, which group together long-term safety follow-ups on various trials where subjects have been exposed to the same therapy. In the coming years, it is likely that the greatest impact on trial status will be these trials having longer follow-up periods.

Figure 10: Ongoing ATMP trials in the UK by clinical Phase year-on-year (2015-2020)
2.12 Consistent split between autologous and allogeneic cell therapy trials

Whilst there has been an increase in the number of all ATMP clinical trials (for both autologous and allogeneic therapies), the proportion of autologous to allogeneic products has remained consistent throughout the years, with approximately 70% being autologous and 30% allogeneic, Figure 11.

Figure 11: Distribution of ongoing autologous and allogeneic cell therapies in the UK clinical trials database from 2015-2020
2.13 Growing number of UK clinical trials sponsored by commercial organisations

Commericially sponsored trials accounted for just under 75% of all UK ATMP clinical trials in 2020, Figure 12. In real numbers this represents a 29% increase in the number of commercially sponsored clinical trials in the last year from 89 to 115.

The number of academic/non-profit clinical trials remains fairly static at 35 – 40 trials per annum, so the increasing proportion of commercial trials reflects the continued growth in commercial trials observed since 2015.

Figure 12: Proportion of academic/non-profit and commercial sponsors of ongoing ATMP clinical trial sponsors from 2015-2020
2.15 Impact of COVID-19 on UK ATMP clinical trials

The true impact of COVID-19 on trial progression is not yet known, however, this pandemic is likely to have delayed trials that were either due to start/initiate or close in 2020. Whilst only one trial has officially been suspended due to COVID-19, individual sites have reported putting trials on hold. Despite good progress to set-up status (Figure 7B), there are still a large number of trials in planning/set-up and a decrease in the number of trials being closed.

When comparing the 2020 published clinical trials database with previous years, it is possible to see the progression of trials through the different trial status. Trials previously reported as being in planning or in set-up have moved into recruiting, and trials previously recruiting have moved to in follow-up or completed. In previous years, there has been a steady increase of trials in recruitment without an increase of trials in planning or in set-up, suggesting that ATMP trials move quickly through planning and regulatory approvals. Even with COVID-19 impacting many aspects of daily life, there has been an increase in the number of trials recruiting. However, unlike previous years, more trials are currently in planning and fewer being closed, suggesting that COVID-19 has potentially slowed the planning, regulatory approval, and recruitment of clinical trials.
3. CGT Catapult UK ATMP clinical trials database - 2020 conclusions

The 2020 CGT Catapult UK ATMP clinical trials database reveals an industry that continues to grow and mature with a significant increase in the number of trials ongoing in the UK, even during the COVID-19 pandemic. The 2020 data continues to demonstrate the year-on-year increase in clinical trials in the UK with 154 trials currently ongoing. This accounts for UK representation in approximately 12% of all global ATMP trials.

Oncology remains the main therapeutic area accounting for 35% of the overall UK ATMP trials ongoing, followed by ophthalmology (12%) and haematology (12%). Similarly, of the trials initiated in 2020, oncology was the largest therapeutic area with haematological indications (19%) and metabolic diseases (18%) being the second and third largest therapeutic areas targeted. This increase in clinical studies targeting metabolic diseases potentially suggests an emerging therapeutic area targeted by ATMPs.

The number of academic/non-profit sponsored trials remains fairly static, however there is a continued increase in commercially sponsored trials year-on-year. Commercially sponsored trials are now accounting for approximately 75% of all UK ATMP clinical trials. The majority of these commercially sponsored trials are backed by non-UK based companies demonstrating the appeal of the UK ecosystem for these types of trials due to the regulatory environment and scientific and clinical expertise available. Gene therapy trials (ex vivo and in vivo) accounted for 70% of all ongoing trials in the UK.

As well as providing CGT Catapult with important information on industry progress, we hope this review serves the advanced therapy community as a resource for planning future clinical programmes.