Cell and Gene Therapy Catapult ATMP clinical trials report 2021

Contents

1. Executive summary

The number of advanced therapy medicinal product[1] (ATMP) clinical trials in the UK continues to increase year-on-year with 168 trials reported as ongoing in 2021, indicating an approximate 9% increase from 2020. Commercially sponsored trials accounted for just under 80% of all UK ATMP clinical trials demonstrating the attractiveness of the UK ecosystem, in particular the Advanced Therapy Treatment Centres (ATTC) network, to commercial sponsors.

The UK is represented in 12% of global ATMP commercial trial activity in all Phases I - III[2], and 9% of all trials. We observed the largest increase in Phase I trials, which grew by 32%, demonstrating successful translation of therapies from non-clinical programs into First-in-Human clinical trials. The majority of ATMP trials are investigating gene therapies (72%), with an even distribution between *in vivo* and *ex vivo* gene therapy trials.

It is important to note that throughout 2020 and 2021 COVID-19 has greatly impacted the routine operations of society, business and healthcare. The MHRA does not need to be notified of interruptions to trials due to COVID-19, therefore the true impact of the pandemic on all stages of clinical trials is not yet completely understood. Fewer trials were reported as completed in 2021 compared to 2020, and this is likely due to the ongoing COVID-19 pandemic, which has resulted in trial delays.

The ATTC network, funded by the UK government Industrial Strategy Challenge Fund, successfully supports the development of the UK infrastructure for clinical adoption of ATMPs. The ATTC network has built, and continues to build, systems within the NHS to ensure that products progress effectively through clinical development and can be commercialised in the UK to reach patients. 55% of UK ATMP trials are being implemented within the ATTC network.

[1]As defined by EC ATMP regulation 1394/2007

[2]Alliance for Regenerative Medicine State of the Industry Briefing 10th January 2022

1.1 Introduction to the 2021 ATMP clinical trials database

The UK 2021 ATMP clinical trials database covers advanced therapy medicinal product (ATMP) clinical trial activities that the Cell and Gene Therapy Catapult (CGT Catapult) understands to be ongoing in the UK as of December 2021. It supersedes the 2020 database and both are available at catapult.org.uk/clinical-trials-database.

The 2021 database has been compiled and verified by the CGT Catapult team, and includes:

- all ATMP trials (see definition of trials included in Section 1.3 Methodology), including non interventional long-term follow-up (LTFU) trials
- academic (which includes non-profit research), and commercial trials
- ongoing trials in the UK, regardless of the geographic location of the sponsor's headquarters

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

The CGT Catapult is an independent innovation and technology organisation committed to the advancement of cell and gene therapies with a vision of a thriving industry delivering life changing advanced therapies to the world. Its aim is to create powerful collaborations which overcome challenges to the advancement of the sector. With over 400 experts covering all aspects of advanced therapies, it applies its unique capabilities and assets, collaborates with academia, industry and healthcare providers to develop new technology and innovation.

The UK ATMP clinical trials database aims to assess the progress and state 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.

A number of countries and organisations now produce reports detailing the current state of clinical trials in the field of "regenerative medicine", of which ATMPs is a specialised subset. These activity reports, however, utilise different methods to identify and analyse trial activity and encompass more than just ATMPs, making global comparisons increasingly difficult. It is important to note that CGT Catapult data may differ from other databases which often include cell therapies which do not fulfil the criteria for ATMPs or may include the same trial in more than one category. To generate our data, we used consistent and systematic methods to interrogate and refine automatically generated data using the comprehensive GlobalData Database. This method identified and removed trials investigating products/therapies not complying with European ATMP definitions (e.g. non homologous use/minimally manipulated products), and also ensured each trial was only counted once in the analysis. It is also important to note that ARM data is significantly different this year compared with previous years with substantially more Asia-Pacific, investigator led and non-commercial trials included than previous years.

1.3 Method

ATMP clinical trials conducted in the UK were identified through a targeted search of GlobalData's clinical trial database[3]. Using these data, trials that did not have a publicly available ID (such as a Clinical Trials or EudraCT number), and which were unable to be verified outside of GlobalData, were then excluded.

The products used in the remaining clinical trials were then assessed for whether they fulfilled the category of ATMPs, as outlined in Directive 2001/83/EC and amended by the ATMP Regulation 1394/2007.

To ensure each trial identified was only counted once in the analysis, products that could fall under the definition of more than one ATMP type were assigned to a single type. For example, a product (such as a CAR-T) that was reported as both a gene and cell therapy in the Global Data database, was counted once as an *ex vivo* gene therapy in this report. Clinical trials investigating multiple indications were also only assigned to a single therapeutic area.

Key trial information was verified using at least one of the following methods:

- Confirmation by Sponsor or other key clinical trial stakeholders (such as participating sites)
- Confirmation in the public domain such as by way of:
    - EU Clinical Trials Register
    - ClinicalTrials.gov
    - ISRCTN Registry
    - NIHR CRN Public Dashboard
    - WHO International Clinical Trials Registry Platform

UK ATMP trials for which key trial information was unable to be verified outside of GlobalData, using one of the methods above, were excluded from the analysis.

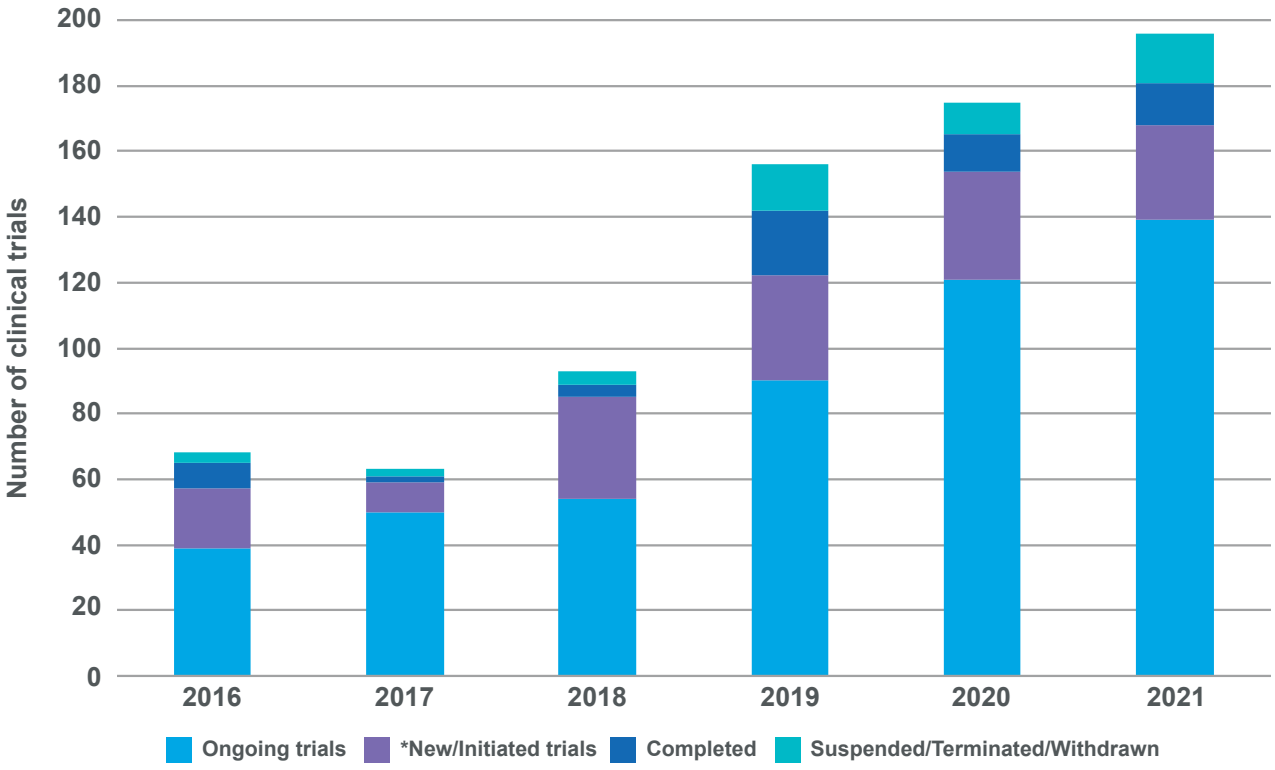
[3] https://www.globaldata.com

2. Commentary on key findings 2021

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

The 2021 UK ATMP clinical trials database shows a continuation of the observed year-on-year increase of ongoing ATMP clinical trials, although growth is slower possibly due to the impact of COVID-19. There were 168 trials ongoing in the UK in 2021, compared to the 154 trials reported in 2020. This represents 9% of all global trials as described in the 2021 ARM report, and 12% of Phase I-III commercial trials. As shown in purple below in **Figure 1**, there has been a slight decrease in trials initiated during 2021 (29) compared to 2020 (33). However, this is likely due to both the ongoing COVID-19 pandemic, which has resulted in delays to trial initiation, as well as reduced visibility for UK activity in 2021 in the public domain in the transition from EudraCT following the UK exit from the EU.

Figure 1: Number of ongoing, initiated, completed, and closed trials 2016-2021

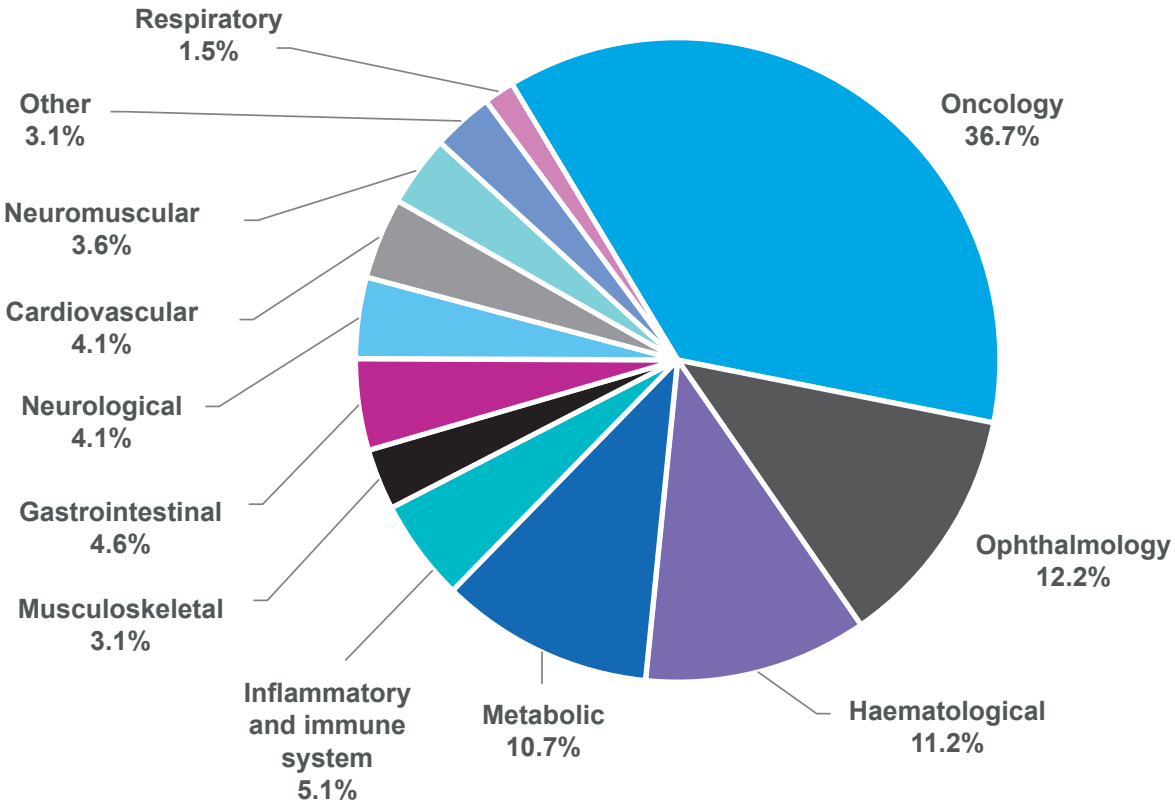


*From 2019, trials shown in purple are trials initiated during that year. For 2016-2018, the designation 'new' includes both trials registered and initiated each year.

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 37% of ATMP clinical trials, followed by Ophthalmology (12%) and Haematological (11%), **Figure 2.**

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



"Other" therapeutic areas, together representing approximately 2.6% of UK ATMP clinical trials, includes dermatological, infectious disease, and renal/urogenital clinical trials.

NOTE: All figures throughout the text of this document are rounded to whole numbers

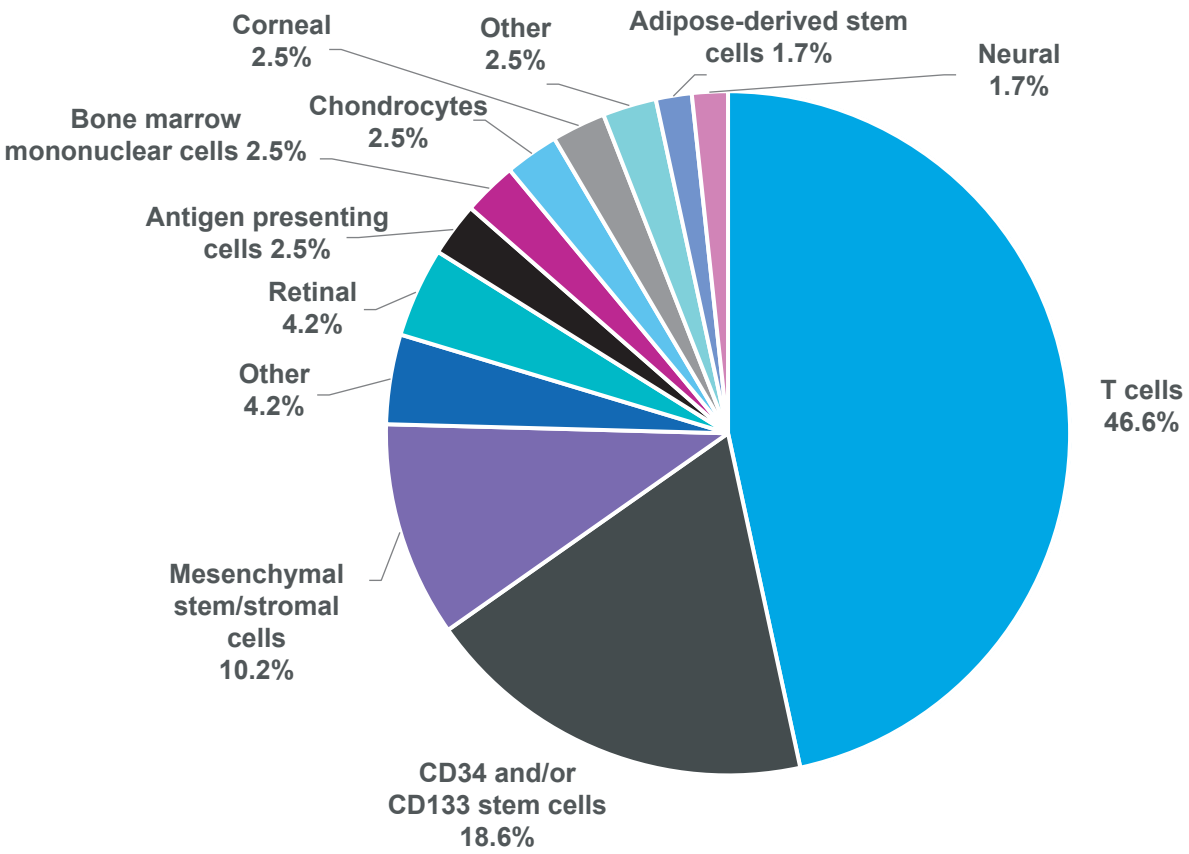
2.2.1 Breakdown of trials initiated by therapeutic area

In addition to being the largest therapeutic area investigated overall, oncology remained the largest therapeutic area of trials initiated in 2021, accounting for 32% of the clinical trials initiated this year. Neurological diseases were the second largest therapeutic area targeted by trials initiated in 2021 (18%). This was followed by trials with therapies targeting metabolic diseases (14%) and ophthalmology (11%), data not shown.

2.3 T cells are the dominant cell type investigated

The cell types investigated in ATMP clinical trials remain largely unchanged from 2020. T cells continue to be the dominant cell type, accounting for 47% 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 by cell type

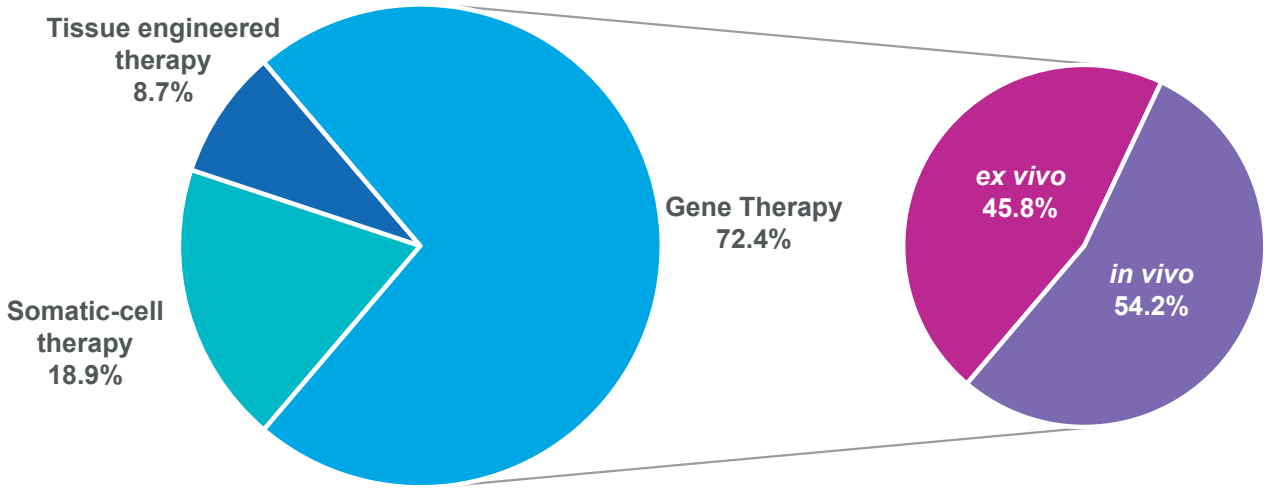


2.4 Majority of therapies in the database are genetically modified

The majority of the 168 ATMP clinical trials ongoing in the UK in 2021 were gene therapies (72%) followed by somatic-cell therapies (19%). Tissue engineered therapies accounted for approximately 9% of the ongoing clinical trials, **Figure 4**.

Of the ongoing gene therapy clinical trials, similar numbers of *ex vivo* (46%), which includes CAR-T, and *in vivo* (54%) genetic modifications were investigated. These gene therapy trials are further discussed in the **Gene delivery technologies** section 2.8.

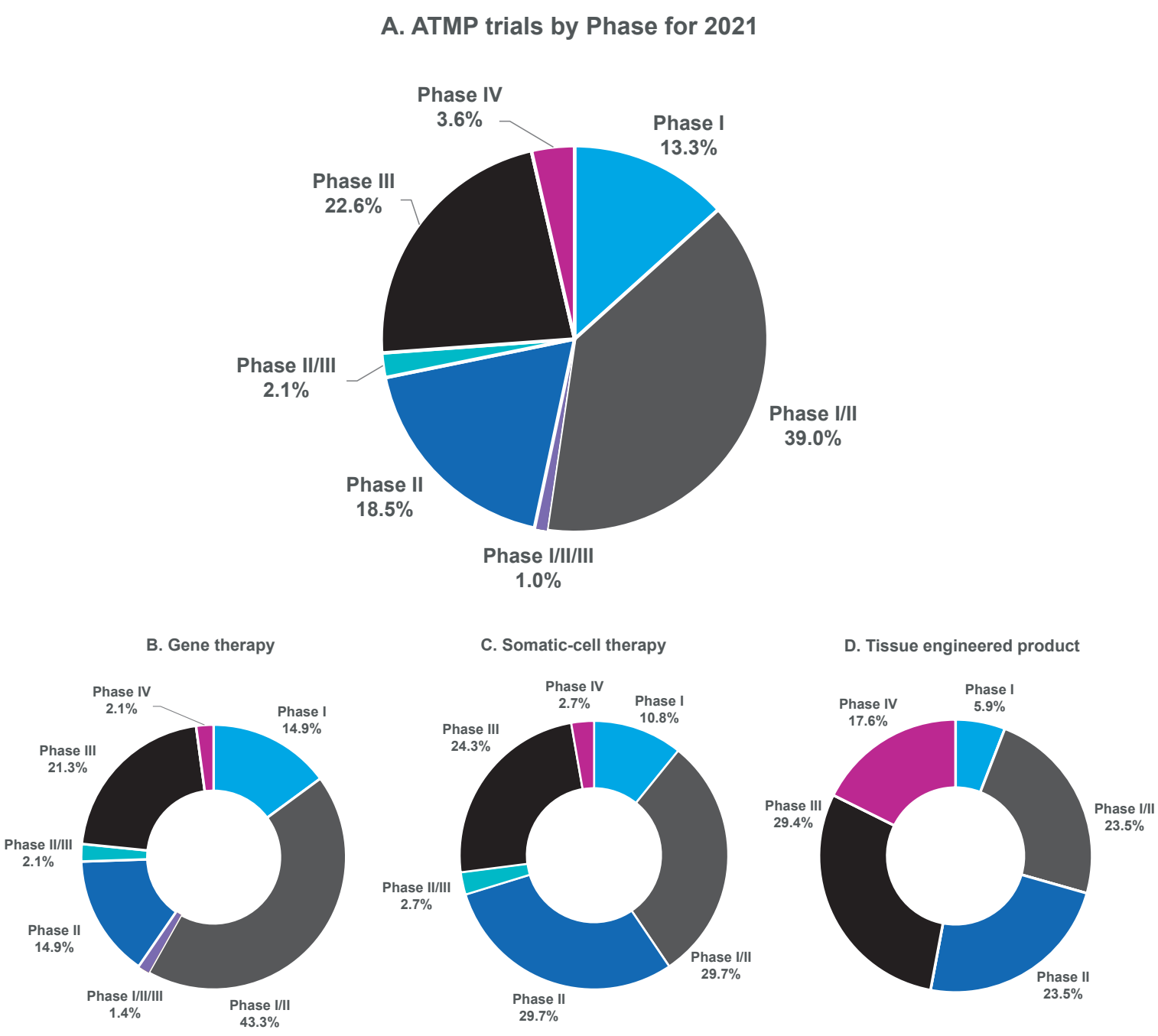
Figure 4: Breakdown of UK ATMP clinical trials by ATMP type



2.5 Breakdown of UK ATMP clinical trials by Phase

The majority of the UK ATMP clinical trials observed in 2021 are in Phase I/II (39%), **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 5 A-D: Breakdown of UK ATMP clinical trials by trial Phase

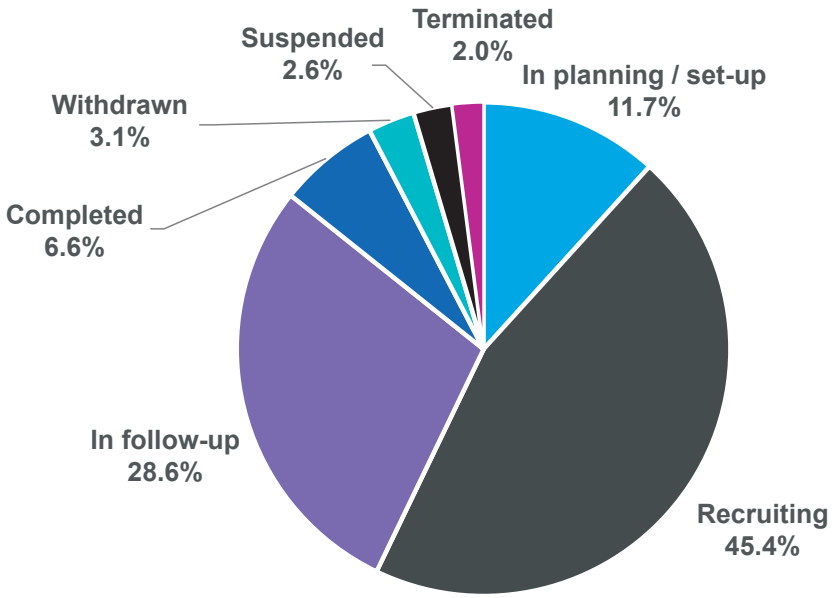


2.6 Breakdown of 2021 UK ATMP trials by status

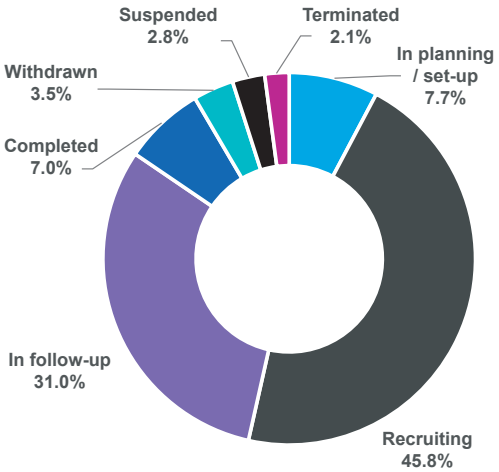
Overall, the majority of the UK ATMP clinical trials ongoing in 2021 are currently recruiting (45%) or in follow-up (29%), **Figure 6A**. All therapy types generally follow the same distribution, **Figures 6B-D**. For tissue engineered products, recruiting trials account for 35% of trials, whilst trials in follow-up account for 29%, **Figure 6D**.

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

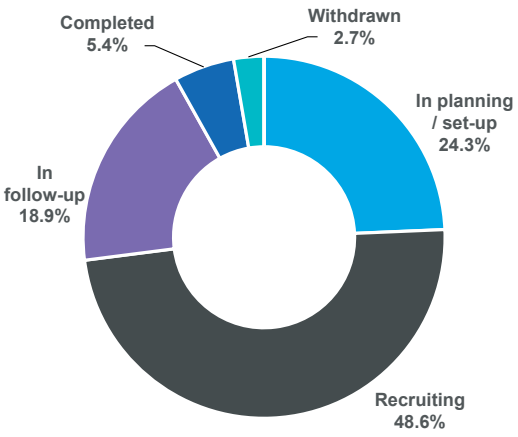
A. Distribution of UK ATMP clinical trials by status



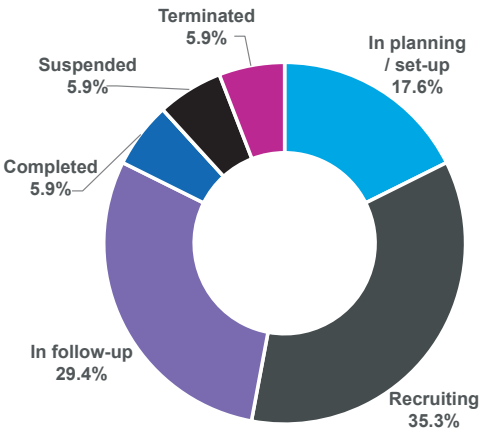
B. Gene therapy trials



C. Somatic-cell therapy trials



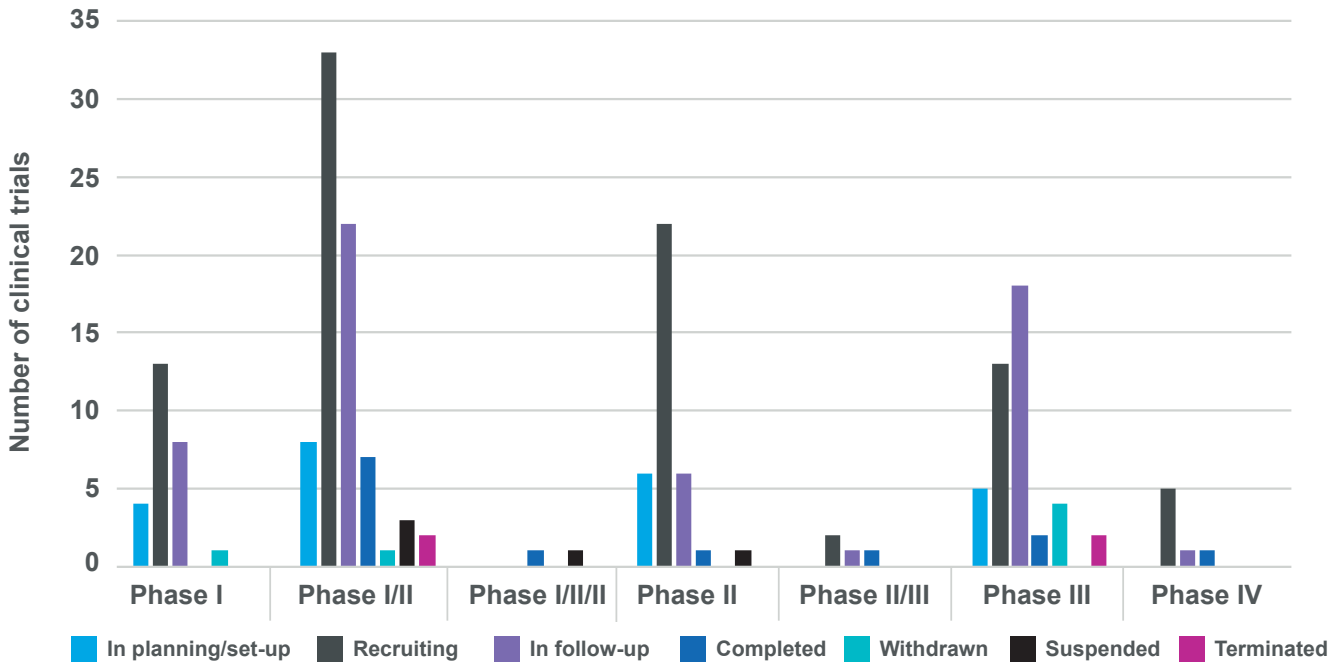
D. Tissue engineered product trials



2.7 Distribution of UK ATMP trials by Phase and status

Of the total UK ATMP clinical trials recruiting in 2021, the majority (33) are Phase I/II, followed by Phase II (22), and Phase I and Phase III (13), **Figure 7**. We observed five Phase IV clinical trials recruiting.

Figure 7: Distribution of UK ATMP clinical trials by trial Phase and status



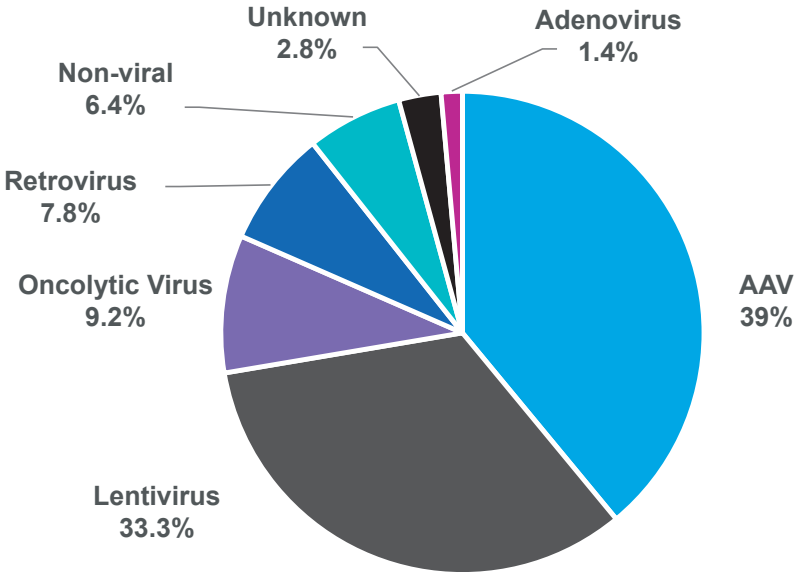
The majority of the trials initiated in 2021 are in planning/set-up (57%), potentially due to the impact of both Brexit and COVID-19 delaying trial initiation, with the rest currently in recruitment. The majority of these newly initiated trials are Phase I/II and Phase III, with eleven and seven trials, respectively (data not shown). 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.

2.8 Gene delivery technologies

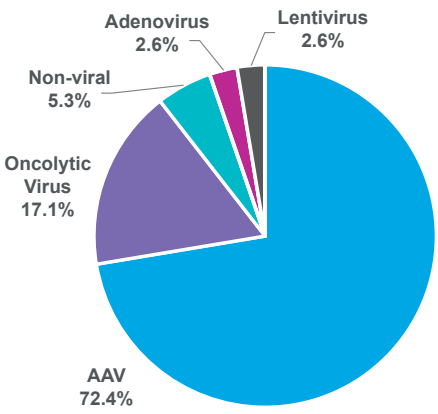
For ***in vivo* gene therapy** clinical trials, AAV based vectors remain the main vector of choice (72%), followed by oncolytic viruses (17%). A small proportion of trials are investigating therapies using non-viral vectors (5%), adenovirus (3%), or lentivirus (3%), **Figure 8B**. For ***ex vivo* gene therapy** clinical trials, the use of lentiviral vector delivery dominates (69%), followed by retroviral vectors (17%), **Figure 8C**. Non-viral *ex vivo* based gene therapies, accounted for 8% of ATMP trials observed.

Figures 8 A-D: Distribution of type and use of gene transfer vectors

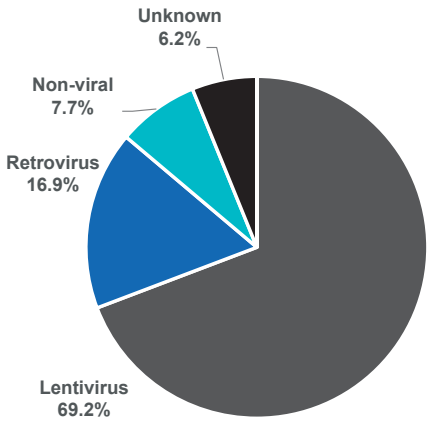
A. Distribution of type of gene transfer vectors used in 2021 ATMP clinical trials



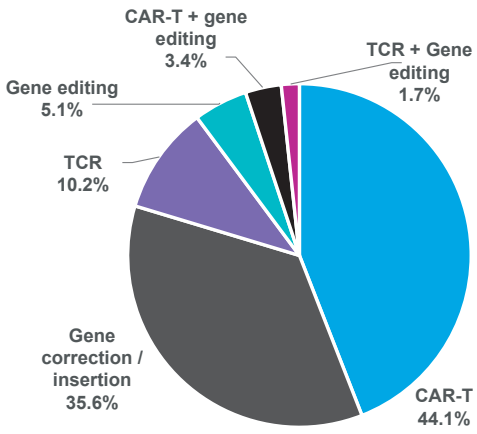
B. Distribution of *in vivo* gene transfer vectors used in 2021 ATMP clinical trials



C. Distribution of *ex vivo* gene transfer vectors used in 2021 ATMP clinical trials



D. Distribution of the type of *ex vivo* gene therapy in ongoing clinical studies



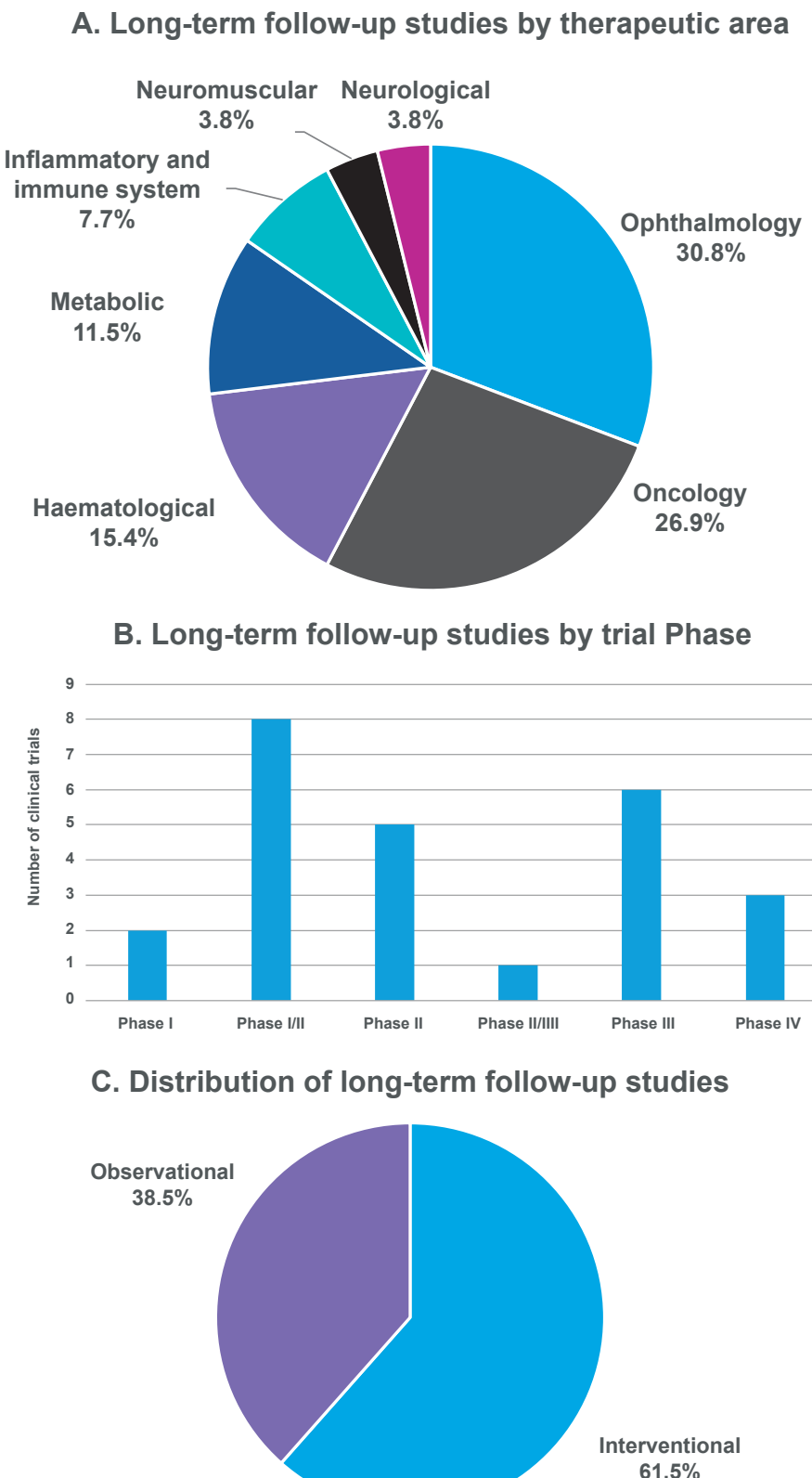
Ex vivo vectors are predominantly used for CAR-T based therapies (CAR-T and CAR-T + gene editing) which account for 44% of *ex vivo* clinical trials. This is followed by "Gene corrections/ insertion" therapies which account for 36%, **Figure 8D**. The *ex vivo* CAR-T and TCR based clinical trials almost exclusively focus on oncology, whilst therapies involving gene corrections target multiple disease types (not shown).

2.9 Long-term follow-up trials

Of the 26 long-term follow-up (LTFU) studies identified, 16 are currently recruiting, 8 are in follow-up, 1 is in planning/set-up, and 1 completed in 2021 (data not shown). Ophthalmology (31%) is the largest therapeutic area for which long-term follow-up trails are ongoing, followed by oncology (27%) and haematology (15%), **Figure 9A**. Together, these account for over 73% of LTFU clinical trials. The majority of these LTFU trials are either Phase I/II or Phase III trials, **Figure 9B**. 62% of the LTFU clinical trials are interventional, **Figure 9C**.

The LTFU trials discussed in this section are distinct trials classified as LTFU, however there also continues to be earlier phase clinical trials which include LTFU as part of their study design, which are not discussed here.

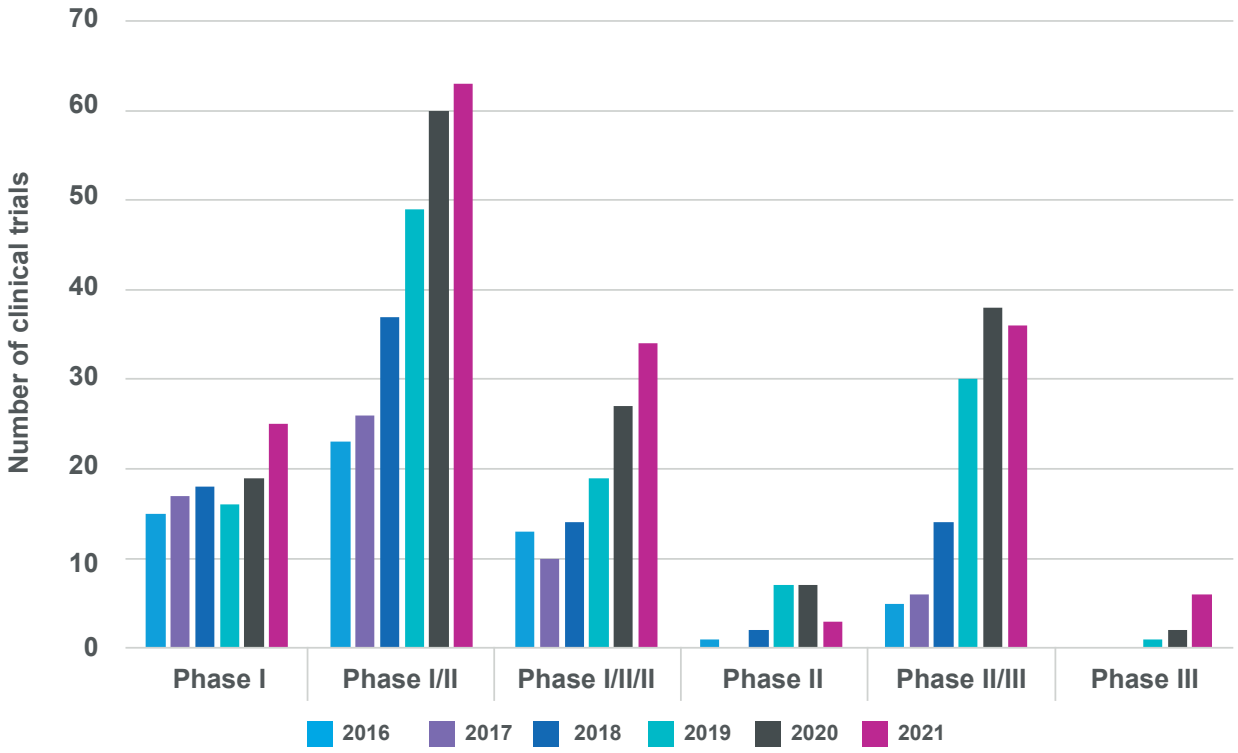
Figure 9 A-C: Distribution of long-term follow-up studies by therapeutic area (A), trial Phase (B), and intervention type (C).



2.10 Growth continues in early phase trials

There has been an increase from 2020 observed in the number of clinical trials across all Phases, with the exception of Phase II/III and Phase III clinical trials, **Figure 10**. The growth seen in 2021 of early phase trials is indicative of the ATMP space growing and successful translation of therapies from non-clinical programs into First-in-Human clinical trials. 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.

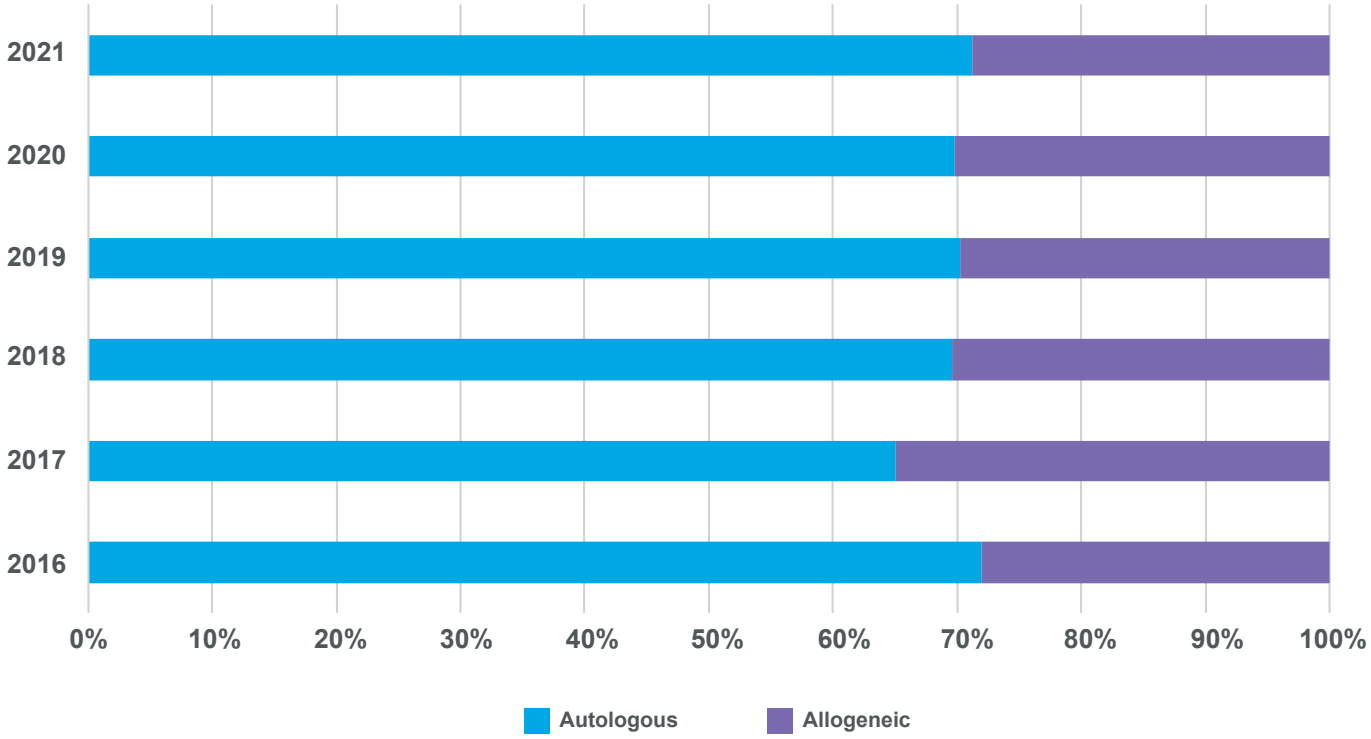
Figure 10: Ongoing ATMP trials in the UK by clinical Phase year-on-year (2016-2021)



2.11 Consistent split between autologous and allogeneic cell therapy trials

There has been an increase in the overall number of ATMP clinical trials (for both autologous and allogeneic therapies) observed as ongoing each year since 2016, however, the proportion of autologous to allogeneic products has remained fairly consistent, with approximately 70% being autologous and 30% allogeneic, **Figure 11**.

Figure 11: Distribution of ongoing autologous and allogeneic cell therapies clinical trials in the UK from 2016-2021



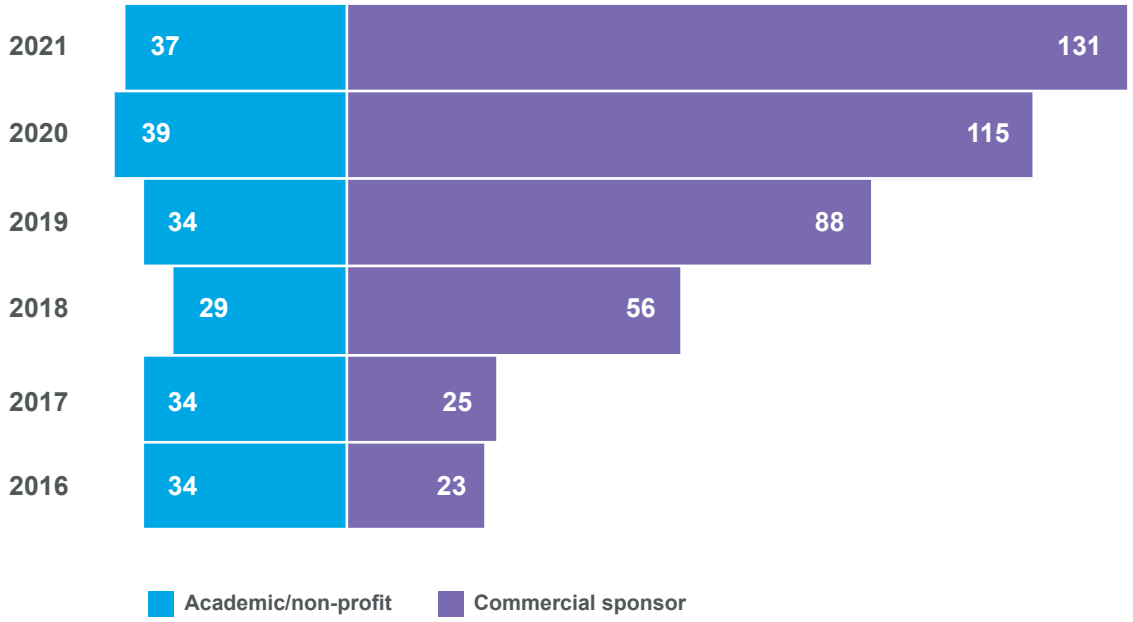
2.12 Growing number of commercially sponsored trials in the UK

Since 2016 and 2017, when the majority of UK clinical trials were supported by academic /non-profit organisations, there has been a strong trend for the emergence of commercial clinical trial sponsorship building from this base.

Commercially sponsored trials accounted for just under 80% of all UK ATMP clinical trials in 2022 demonstrating the attractiveness of the UK ecosystem, in particular the ATTC Centre network, to commercial sponsors.

This year we saw a 13% increase in the number of commercially sponsored clinical trials from 115 to 131, **Figure 12**. Whereas the number of academic/non-profit clinical trials continues to remain fairly static year-on-year.

Figure 12: Numbers of academic/non-profit and commercial of ongoing ATMP clinical trial from 2016-2021



3. Favourable ecosystem for ATMP trials in the UK

The Advanced Therapy Treatment Centres network (ATTC;(https://www.theattcnetwork.co.uk/)), coordinated by the CGT Catapult, continues to grow and provide more developers of advanced therapies with a clear route to adoption and commercialisation within the UK. This is essential for the potential of these therapies to be realised and for the UK to achieve the ambition of building a world leading advanced therapy industry and maximising patient access to these therapies. As of February 2022, the ATTC network consists of 114 organisations, including 25 NHS Trusts and 59 ATMP industry partners. The proportion of ongoing clinical trials run via the dedicated ATTC network has increased consistently both in the UK (from 39% to 55% over 4 years) and globally (from 2% to 5%).

4. CGT Catapult UK ATMP clinical trials database – 2021 conclusions

The 2021 CGT Catapult UK ATMP clinical trials database reveals an industry that continues to grow and mature with an increase in the number of trials ongoing in the UK, even during the COVID-19 pandemic and post Brexit. The 2021 data continues to demonstrate a year-on-year increase in clinical trials in the UK with 168 trials currently ongoing. This represents 9% of all global trials and 12% of Phase I-III commercial trials, as described in the 2021 ARM report.

There has been a further increase in commercially sponsored trials, now accounting for approximately 80% of all ATMP trials in the UK. This increase reflects the favourable landscape for ATMP trials in the UK, supported by investments and partnerships fostered by the Advanced Therapy Treatment Centres network and other UK government led initiatives.

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