Optimising the design of clinical trials for advanced therapies

Summary findings from workshop
4 September 2019
Introduction

On 4 September 2019 we held a workshop to address, in an open and unattributed way, the challenges of conducting clinical trials with ATMPs in the UK NHS system.

This document summarises the outputs.

Organisations represented

- Association of British Pharmaceutical Industry
- Academy of Medical Sciences
- Adaptimmune
- Addenbrooke’s Hospital
- AstraZeneca
- BioIndustry Association
- Cancer Research UK
- Cell Medica
- Cell and Gene Therapy Catapult
- Department of Health and Social Care
- Freeline Therapeutics
- GlaxoSmithKline
- Health Research Authority
- iMATCH - Manchester Advanced Therapy Treatment Centre
- Immetacyte Ltd
- Innovate UK / UKRI
- Janssen J&J
- Knowledge Transfer Network
- London Advanced Therapies
- MedCity
- Medicines and Healthcare products Regulatory Agency
- Midlands Wales - Advanced Therapy Treatment Centre
- National Institute for Health and Care Excellence (NICE)

- National Institute for Health Research
- NHS England
- NHS Scotland
- NHS Specialist Pharmacy Service
- NHS Wales
- NIHR Office for Clinical Research Infrastructure
- Northern Alliance - Advanced Therapies Treatment Centre
- Oxford Biomedica
- Skerne Medical Group
- University College London
- Videregen
Challenges

- Operational
- Clinical trial design
- Trial coordination activities
- Reimbursement considerations
Operational themes
Recurrent operational themes

Only a limited number of sites are capable of performing ATMP trials effectively and efficiently.

Sites have different governance and administrative requirements which can slow and defer approaches by developers.

Sites without prior experience with advanced therapies find it hard to gain the necessary knowledge and resource to conduct trials.

The complexity and variety of these products act to slow uptake and trials, e.g. the labelling, packaging and local reconstitution methods vary widely.
Addressing operational themes

1. Increase the number of study sites capable of performing studies with ATMPs by developing specialist centres and generating a skilled workforce in the NHS

2. Develop baseline standards to conduct research at sites

3. Create a “best practice” group of stakeholders to share knowledge and experience

4. Work with industry to standardise methods to reduce variability in products and delivery requirements
Trial design themes
Recurrent themes in trial designs

Sponsors are hesitant to present **novel study designs** to the MHRA in case this results in delays in trial approvals.

It is difficult to develop a **critical mass of knowledge** - principally due to rare diseases often being the focus for trials of advanced therapies.

Trials designs can have **rigid treatment regimes** after administration that are not patient focussed and do not allow for flexibility for individuals’ responses.

It may not be practical to generate **dose response profiles** with small numbers of patients and variable products.
### Addressing challenges in trial designs

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<thead>
<tr>
<th>Novel study designs</th>
<th>Critical mass of knowledge</th>
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<tbody>
<tr>
<td>• Meet with the MHRA and REC early in development</td>
<td>• Stratify patients to reduce trial sizes</td>
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<td>• Articulate clear stop signals for studies</td>
<td>• Have centres of excellence conduct trials across multiple indications to build experience with administration of ATMPs</td>
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<td>• Ensure clear communications with clinical teams and regulators</td>
<td>• Pool data across indications, where appropriate, to inform risk/benefit profiles</td>
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<td>• Build in flexibility for treatment regimes post administration to address variability in patient responses</td>
<td>• Use patient specific biomarkers to demonstrate changes after administration</td>
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<td>• Allow patients to leave hospital facilities after CAR-T administration if risk / benefit profile is favourable</td>
<td>• Consider the use of basket trials with a single product</td>
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<tr>
<th>Dose response profiles</th>
<th>Rigid treatment regimes</th>
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<tr>
<td>• Early detailed characterisation of starting material and Drug Products in development to allow extrapolation of dosing</td>
<td>• Work with collaborators to present hypothetical trial designs to MHRA for comment</td>
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<tr>
<td>• Have flexibility and pragmatism in dosing regimes with a focus upon patient safety as well as efficacy</td>
<td>• Work collaboratively with REC, NHS R&amp;D and MHRA to develop frameworks to support flexibility of design</td>
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Trial coordination themes
Recurrent trial coordination themes

- Trials of advanced therapies can cause **disruption across departments** versus standard clinical pathways.

- There may be **limited opportunities to collect source tissues** as patients progress in their care pathways.

- There is often **poor communication between manufacturing and clinical sites** which can affect treatment protocols and scheduling procedures.

- Disease progression may affect **viability of source tissue** and the efficacy of the final drug product.

- There are **potential gaps in the logistics chain** that create risks in the safe delivery of products and their administration.
Addressing trial coordination themes

- Link up multi-disciplinary teams and lead coordinated approaches
- Integrate cell and tissue procurement into the patient care pathway
- Integrate clinical, manufacturing, tracking and tracing to optimise information flow
- Develop advanced diagnostics and characterisation for patient selection and product release
- Perform process mapping and trial runs for logistics and sites upon receipt
Reimbursement considerations
Recurrent themes - reimbursement

Global agencies have different approaches to assessment, but are all interested in incremental clinical effectiveness.

Clinical trials are the primary source of data demonstrating this effectiveness.

Besides securing reimbursement for ATMP acquisition costs, hospitals also need to be reimbursed for all other costs they incur in delivering a therapy.

Managed entry agreements can help address data uncertainty at launch; modelled data could also play a role.

Engagement with HTA bodies should be done earlier in development than with traditional pharmaceuticals, to ensure evidence generation plans address their requirements.
Addressing the adoption of ATMPs

Understand how post-launch evidence generation can support adoption

Improve the quality of design and execution of clinical trials

Consider type of managed entry agreement that can address data uncertainty and affordability issues

Understand levels of uncertainty that are acceptable to HTA bodies at the time of registration

Seek early scientific advice in multiple territories to define required data
Moving forward
Cross-industry engagement

Utilise the ATTC and LAT Networks to develop solutions to challenges

All stakeholders to actively collaborate to optimise the design, execution, analysis and settings of clinical trials to make the UK a preferred territory for research

Developers to approach the MHRA and NICE for advice early in development

There is a need to simplify the roadmap for ATMP studies to reduce time and costs especially for SMEs with limited time and resources

Both industry and the NHS need to start developing facilities, manufacturing and staffing now to avoid bottlenecks in the near future
Next steps

- Develop systems to match the complexity of a clinical ATMP study to the capabilities of a hospital site.
- Create vehicles for industry to present workshops on innovative study designs for discussions with the MHRA.
- Organise and facilitate workshops with regulators and key market access stakeholders to explore how innovative clinical trial designs that address the needs of ATMPs can meet regulatory and reimbursement requirements.
- Create a central information hub to support developers and clinical sites.
This project has been funded by the Industrial Strategy Challenge Fund, part of the government's modern Industrial Strategy. The fund is delivered by UK Research and Innovation.