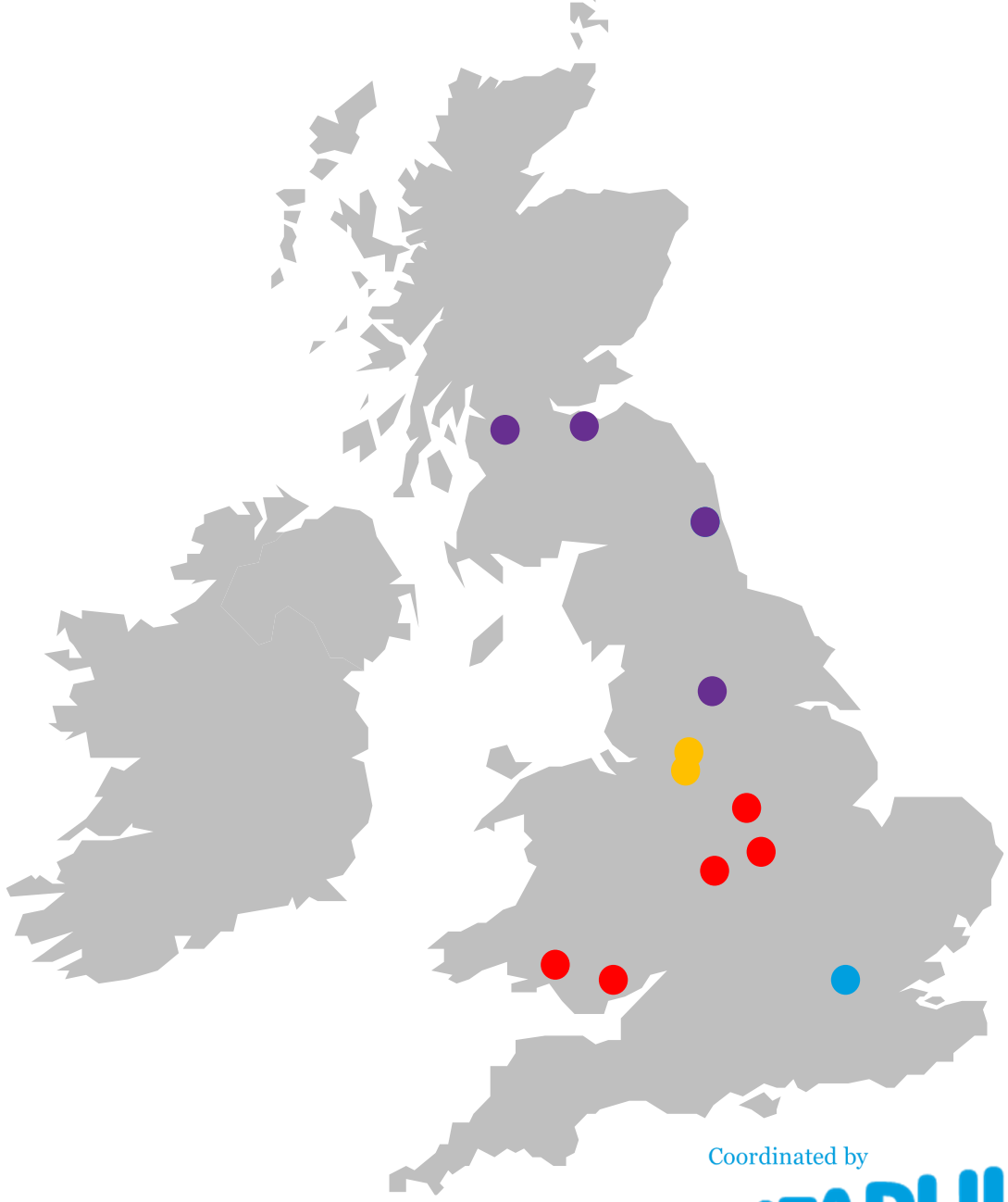
Advanced Therapy Treatment Centres

Optimising the design of clinical trials for advanced therapies

Summary findings from workshop
4 September 2019



INDUSTRIAL STRATEGY

UK Research and Innovation

Coordinated by CATAPULT Cell and Gene Therapy

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

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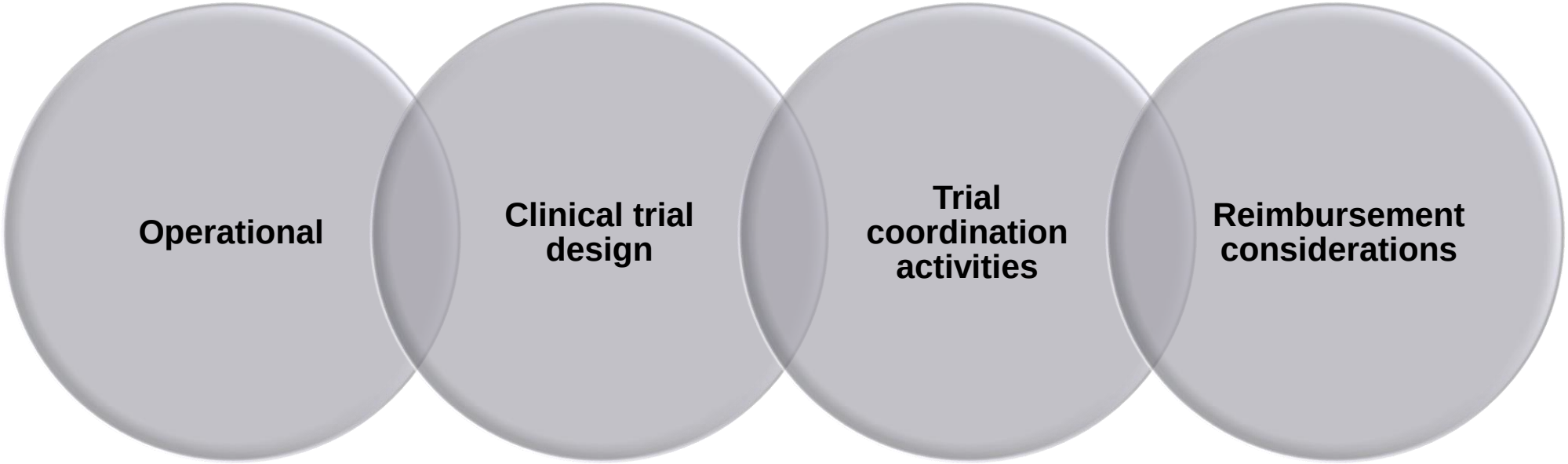
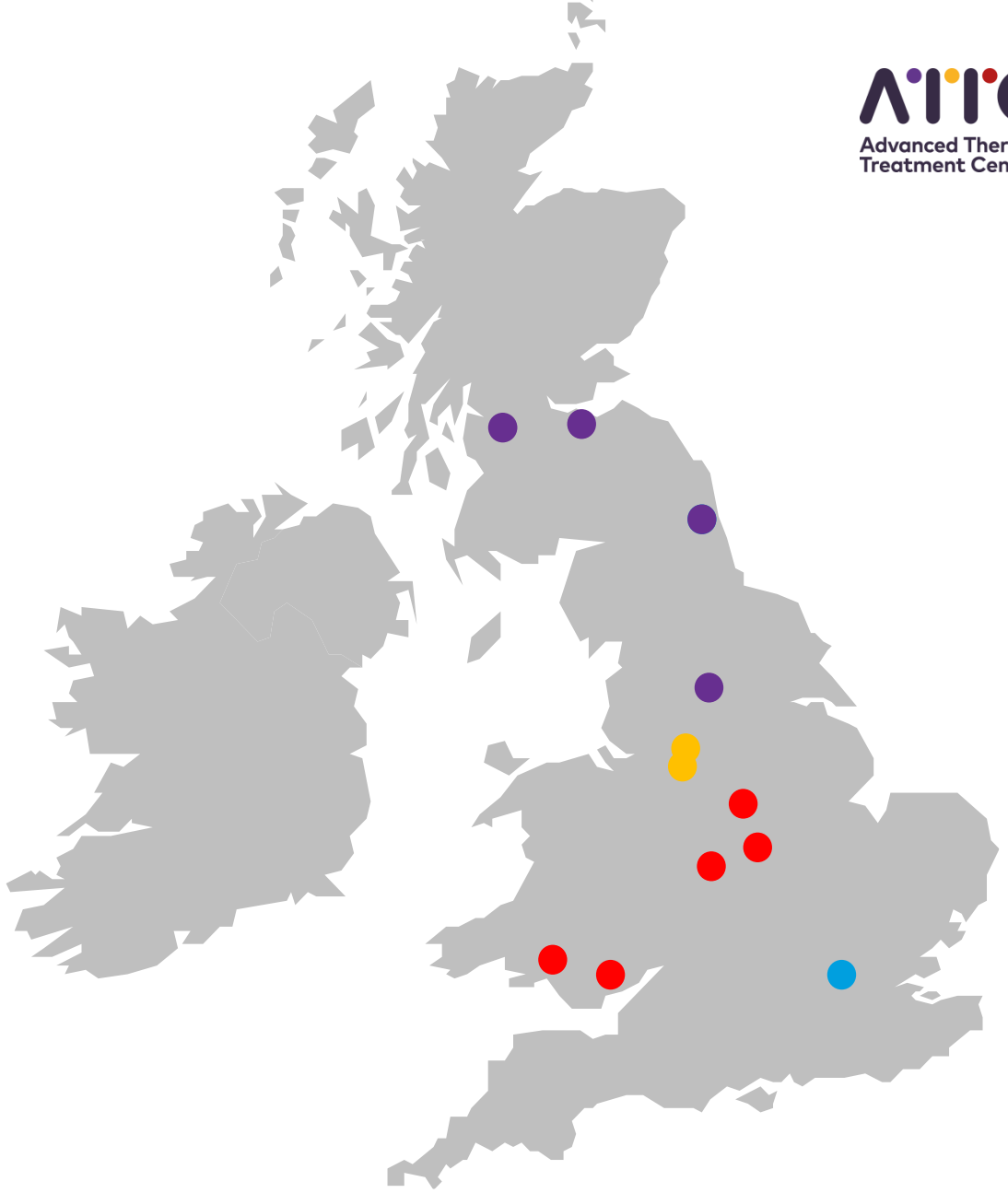
Challenges


Operational
Clinical trial design
Trial coordination activities
Reimbursement considerations

Operational themes



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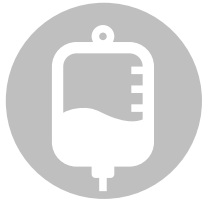
Recurrent operational themes

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



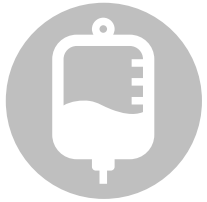
The **complexity and variety of these products** act to slow uptake and trials, e.g. the labelling, packaging and local reconstitution methods vary widely

Addressing operational themes

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

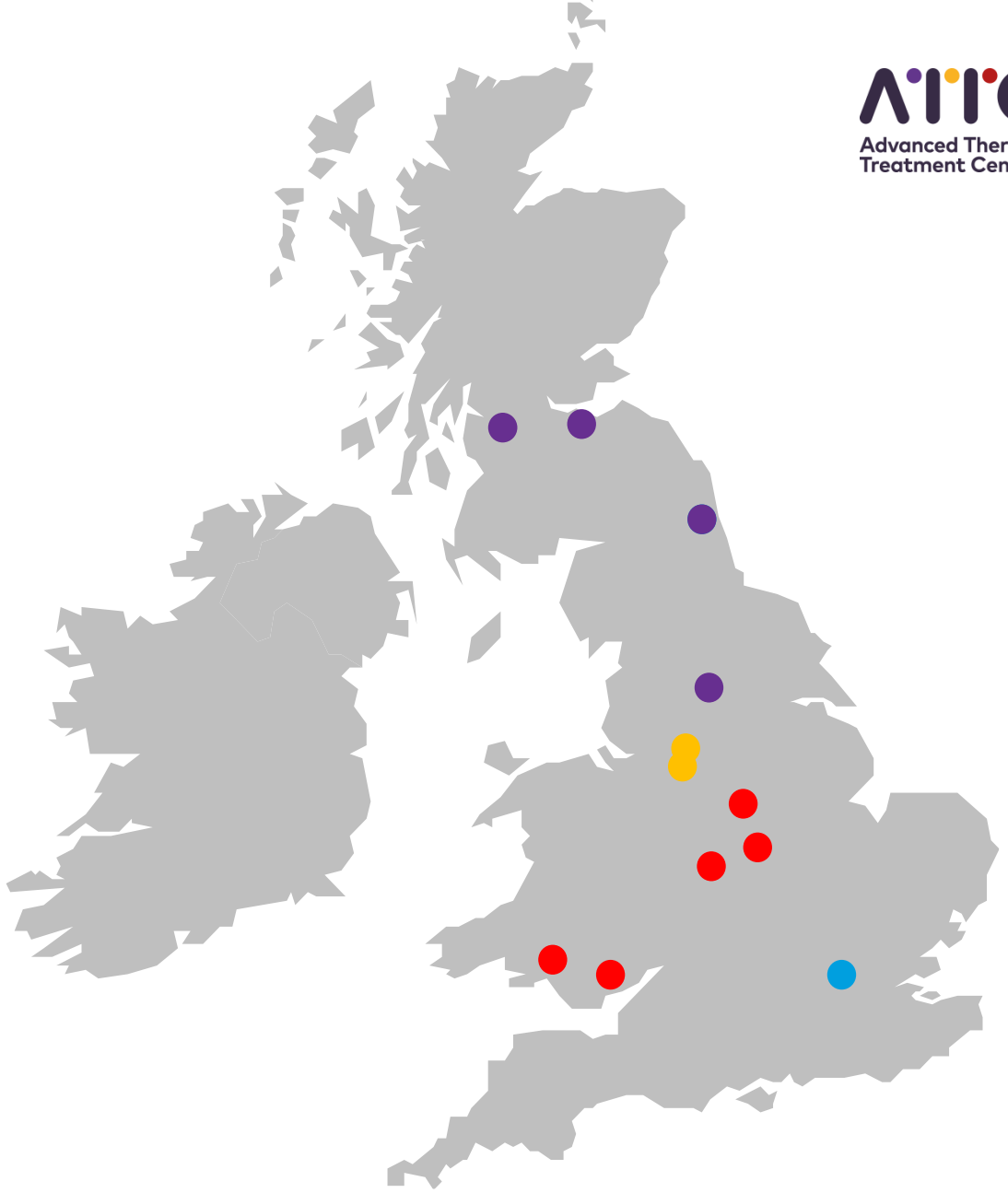
Develop baseline standards to conduct research at sites

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



Work with industry to standardise methods to reduce variability in products and delivery requirements

Trial design themes



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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

Novel study designs

- Meet with the MHRA and REC early in development
- Articulate clear stop signals for studies
- Ensure clear communications with clinical teams and regulators
- Build in flexibility for treatment regimes post administration to address variability in patient responses
- Allow patients to leave hospital facilities after CAR-T administration if risk / benefit profile is favourable

Critical mass of knowledge

- Stratify patients to reduce trial sizes
- Have centres of excellence conduct trials across multiple indications to build experience with administration of ATMPs
- Pool data across indications, where appropriate, to inform risk/ benefit profiles
- Use patient specific biomarkers to demonstrate changes after administration
- Consider the use of basket trials with a single product

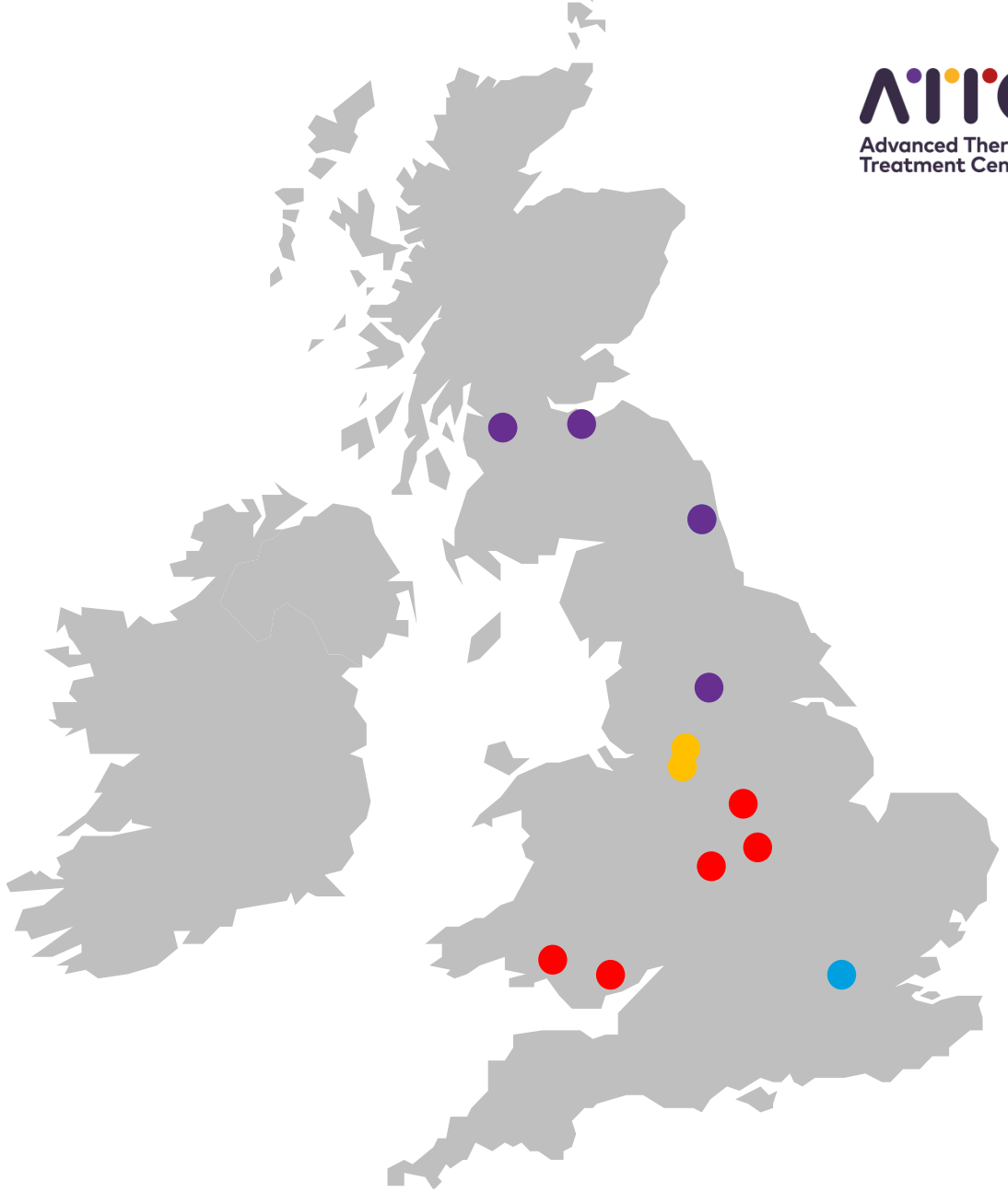
Dose response profiles

- Early detailed characterisation of starting material and Drug Products in development to allow extrapolation of dosing
- Have flexibility and pragmatism in dosing regimes with a focus upon patient safety as well as efficacy

Rigid treatment regimes

- Work with collaborators to present hypothetical trial designs to MHRA for comment
- Work collaboratively with REC, NHS R&D and MHRA to develop frameworks to support flexibility of design

Trial coordination themes



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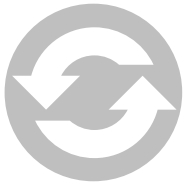
Recurrent trial coordination themes

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

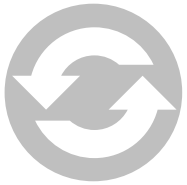
Disease progression may affect **viability of source tissue** and the efficacy of the final drug product

There are **potential gaps in the logistics chain** that create risks in the safe delivery of products and their administration

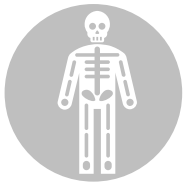
Addressing trial coordination themes

Link up multi-disciplinary teams and lead coordinated approaches

Integrate cell and tissue procurement into the patient care pathway



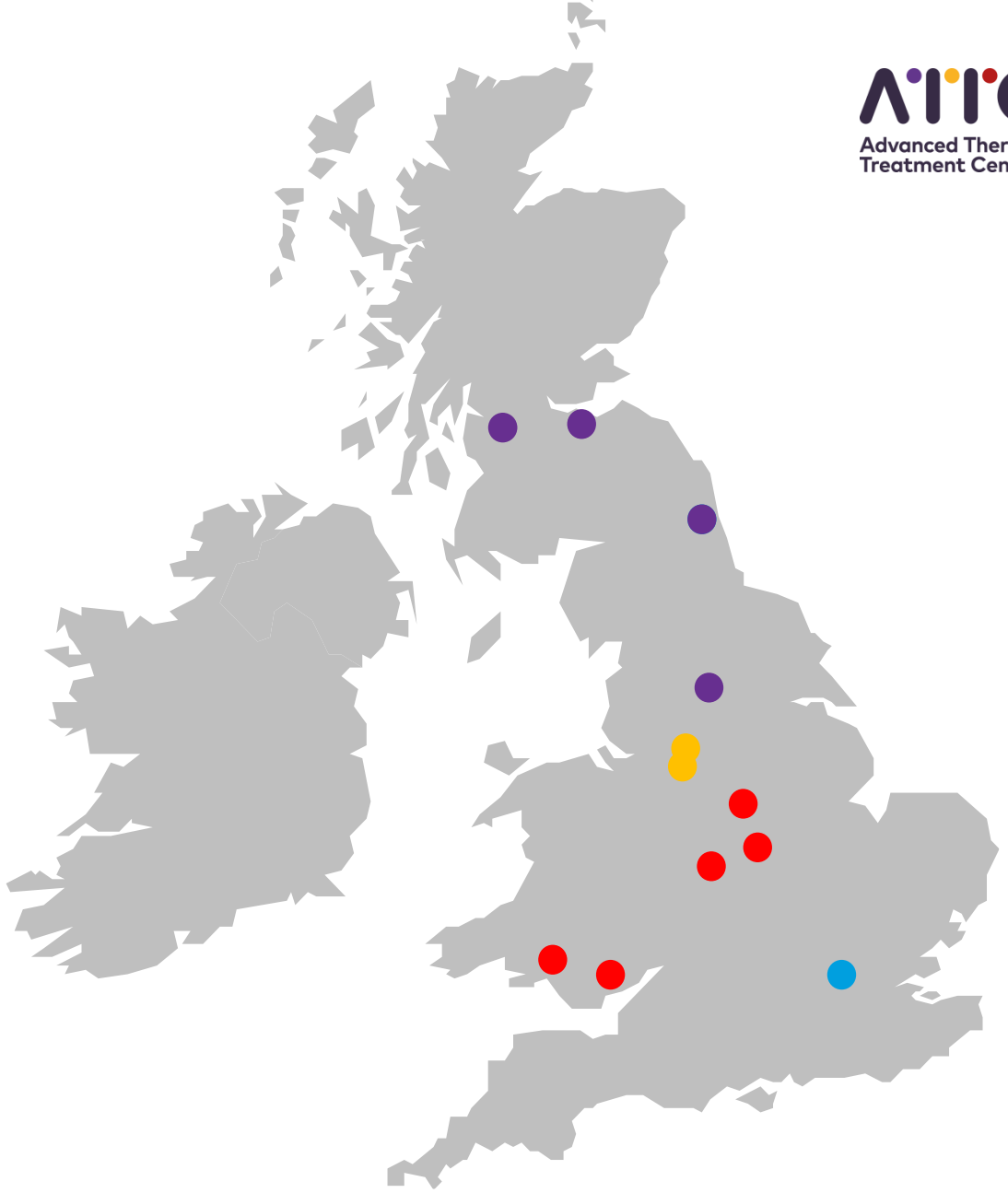
Integrate clinical, manufacturing, tracking and tracing to optimise information flow



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



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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

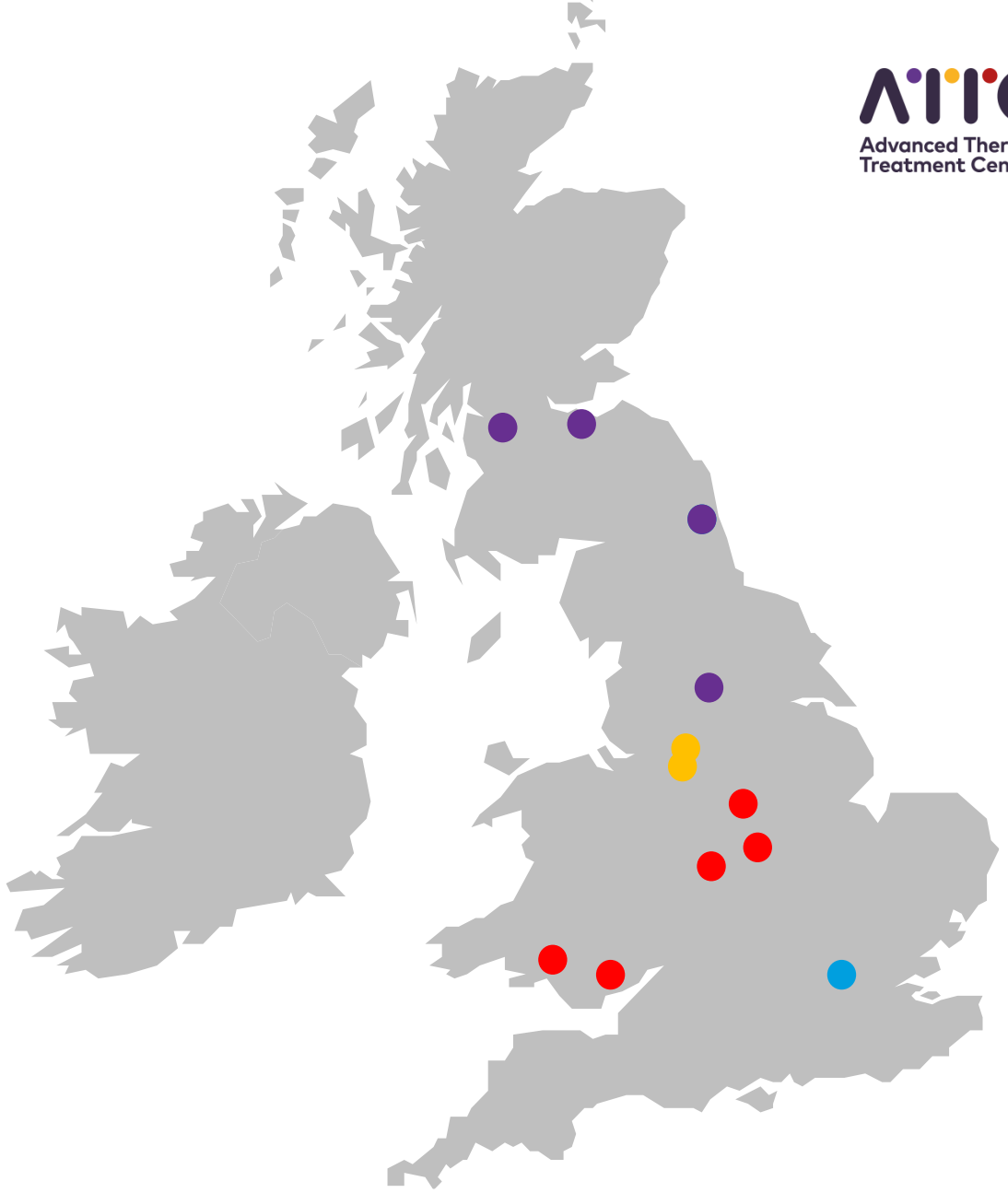
Improve the quality of design and execution of clinical trials

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



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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

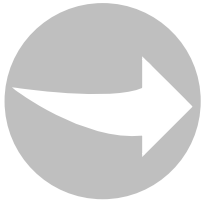
Both industry and the NHS need to start developing facilities, manufacturing and staffing now to avoid bottlenecks in the near future

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.

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https://www.theattcnetwork.co.uk/

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