Applying Quality by Design to Cell and Gene Therapies
About CGT Catapult

Part of a world-leading network of technology and innovation centres

Provide access to unique technical facilities and expertise to help adopt, develop and exploit innovations

Bridge the gap between businesses and academic research

Established by Innovate UK as a not-for profit, independent centre

It is our vision for the UK to be a global leader in the development, delivery and commercialisation of cell and gene therapies.

Where businesses can start, grow and confidently develop advanced therapies, delivering them to patients rapidly and effectively.
CGT Catapult Capability:

**Accelerate**
- the commercialisation of innovations from research

**Complement**
- industry and academia with unique technical facilities and expertise

**Innovate**
- in collaboration with academia and industry

**Facilitate**
- operating in UK as a global centre; working with Government, the NHS and international regulators

**Development laboratories**
- 1200m² purpose built centre
- Analytical characterisation
- Process development
- Viral vector

**Manufacturing centre**
- 7000m² manufacturing centre designed specifically for cell and gene therapies
- 12 segregated large clean room modules
- Secure supported collaboration model
- Centre of a cell and gene therapy cluster

**Cell and gene therapy specialists (>180)**

**Industrialisation**
- Process development
- Analytical development
- Manufacturing systems
- Supply chain

**Regulatory and clinical development**
- Regulatory
- Non clinical safety
- Clinical delivery
- Programme management

**Engagement**
- Collaboration formation
- Intellectual property and patent
- Health economics
- Reimbursement
Breaking down industry barriers

Manufacturing and supply chain
- Ability to scale up cost effective, robust and reliable manufacturing
- Meaningful quality and analytical assays
- Specificity of storage and delivery systems

Regulatory and clinical framework
- Uncertain, complex regulatory environment
- Clinical trial site ability to handle live products
- Cautious hospital research committees

Health economics
- Uncertainty on reimbursement
- Poorly understood health economics
- Unproven business models
## Industrialisation

### The challenge

Developing a reliable and robust manufacturing process.

### How we can help

- Identifying ways to lower the costs of manufacturing your product.
- Finding innovative ways to make your process more efficient and robust.
- Providing methods to accelerate and support clinical trials.
- Helping ensure your process and product are controlled and quality compliant.
- Using tried and tested methods to transfer seamlessly to Good Manufacturing Practice (GMP) manufacturing.
The Industrialisation Team - Our team is your team

- Cell Characterisation
- Potency Assay Development
- In-Process Controls
- Data Mining and Informatics

- GMP Compliance
- GMP Knowledge Base
- CMC
- Documentation

- Design Space
- CPPs for CQAs
- Scale-up / Automation
- Closed Processing
- In-Process Controls
- Process Economics
- Device Design

- Vector Design / Optimisation
- Large Scale production
Cell and Gene Therapies – a Brief Overview
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Cost</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yescarta (axicabtagene ciloleucel)</td>
<td>$373,000</td>
<td>Kite’s CAR-T therapy for forms of Diffuse large B-cell lymphoma (DLBCL) in adults. Type of non-Hodgkin lymphoma (NHL).</td>
</tr>
<tr>
<td>Strimvelis (GSK’s treatment for a very rare disease called ADA-SCID (Severe Combined Immunodeficiency due to Adenosine Deaminase deficiency),</td>
<td>€600,000</td>
<td></td>
</tr>
<tr>
<td>Kymriah (tisagenlecleucel)</td>
<td>$475,000</td>
<td>Novartis’s CAR-T therapy for B-cell precursor acute lymphoblastic leukemia (ALL) in children and young adults.</td>
</tr>
<tr>
<td>Glybera (alipogene tiparvovec)</td>
<td>&gt;€1,000,000</td>
<td>UniQure’s AAV-based gene therapy to treat the rare inherited disorder lipoprotein lipase deficiency (LPLD)</td>
</tr>
</tbody>
</table>
### State of Play in the EU – Since Regulation (EC) 2007/1394

<table>
<thead>
<tr>
<th>Product</th>
<th>Status Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imylic</td>
<td>Approved 2015</td>
</tr>
<tr>
<td>Holoclar</td>
<td>Approved 2015</td>
</tr>
<tr>
<td>Strimvelis</td>
<td>Approved 2016</td>
</tr>
<tr>
<td>Strimvelis</td>
<td>(2 patients treated – patients go to Italy for treatment)</td>
</tr>
<tr>
<td>Zalmoxis</td>
<td>Approved 2016, Conditional MA</td>
</tr>
<tr>
<td>Chondroselect</td>
<td>Voluntary Withdrawal 2016</td>
</tr>
<tr>
<td>MACI</td>
<td>Approved 2013, Suspended 2014</td>
</tr>
<tr>
<td>Provenge</td>
<td>Approved 2013, Withdrawn 2015</td>
</tr>
<tr>
<td>Glybera</td>
<td>Approved 2012, Voluntary Withdrawal 2017</td>
</tr>
</tbody>
</table>
Immuno-Oncology Sector – The Next Generation!

*Adapted from the original presented at Wells Fargo Securities Healthcare Conference, Nov 2017

Need to deliver scalable, low cost manufacturing solutions to enable healthcare provider adoption of a diverse portfolio of therapies.
What key factors influence therapy price?

Key Cost Contributors – Product Manufacture and Administration

Primary focus of today’s talk

Key Cost Contributors – Perceived / Tangible value to the Healthcare System

- Can be very challenging to define
- What is the true cost (lifetime cost) of a patient to the healthcare system
- How do you engage a patient for their lifetime, especially if they are cured within a year?
Our Development Strategy

A Risk and Cost Based Approach
Quality by Design

“A systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management (ICH Q8(R2))”

Q8
Pharmaceutical Development
Application of systems to support the development and manufacture of DS and DP throughout the product lifecycle

Q9
Quality Risk Management
- Bring risk management into Pharma industry
- Provide details of systematic approach to QRM
- Info on QRM tools to enable effective risk based decisions

Q10
Pharmaceutical Quality Systems (PQS)
- Achieve Product Realisation
- Establish and Maintain a State of Control
- Facilitate continual improvement
Understanding your product

Product Characterisation & Baseline Process

- **Target Product Profile**: Indication, treatment, delivery mode, dose, formulation efficacy, side effects
- **Quality Target Product Profile**: Quality characteristics to ensure safety and efficacy as promised in the label

Process Optimisation & Scaling

- **Critical Quality Attributes**: A physical, chemical or biological, property that should be within an appropriate limit, range to ensure product quality
- **Critical Process Parameters**: Process parameter whose variability should be monitored or controlled to ensure the process produces the desired quality

Process and Analytical Development
Understanding the needs of your stakeholders

**Stakeholders**
- Clinic
- Investors
- Regulators
- Manufacturing

**Process / Manufacturing Development**
- Short Term
  - Risk to Patient / Product Variations / Failed Manufacture
  - Not Cost Prohibitive
  - Safety / Understanding / Control
  - Design Space / Robust and Reproducible

**Phase I/II Clinical Trials**

**Long term**
- Commercialisation
- Ease-of-use
- Economic/ Commercial Viability
- Full Characterisation / GMP Compliance / IPCs
- Automation and High-Throughput
Understanding your process

Process Mapping

Ishikawa

Areas of process currently undefined

Risks and Mitigation Strategies

Root Cause of Failure

Facility Utilisation and CoGs

FMEA

Facility Utilisation Profile
**Knowledge Space, Design Space and Control Space**

**Knowledge Space** - What you have tested and what you know.

**Design Space** - What works – the CPPs that give you the desired CQAs.

**Control Space** - Bandwidth allowed around optimal operation.

- **Documentation** - SOPs / Working Instructions / Batch Manufacturing Records
- **Process Control** - Monitoring / Analytics / IPCs / Decision Trees
- **Experimentation** - Screening Studies / Optimisation / Alternative suppliers / New Technologies
### Identifying areas of development focus.

<table>
<thead>
<tr>
<th>Area</th>
<th>Focus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Raw Material Supply</strong> (e.g. Adv. agent)</td>
<td>Needs of the clinic versus needs of the market / Skilled work-force</td>
</tr>
<tr>
<td><strong>Closed Processing</strong> (e.g. Technology Selection)</td>
<td>Manufacturing strategy / Clinical population needs</td>
</tr>
<tr>
<td><strong>Automation</strong> (e.g. Throughput/accuracy)</td>
<td>Data Integrity and Storage (e.g. Electronic Record Keeping and Tracking)</td>
</tr>
<tr>
<td><strong>Adaptive Control</strong> (Process robustness)</td>
<td>Facility Throughput</td>
</tr>
<tr>
<td><strong>Process Control</strong> (e.g. In line analytics)</td>
<td>Clinical Handling (Specialised thaw-at-site systems)</td>
</tr>
</tbody>
</table>

### Additional Areas
- **Intermediate / Product Stability**
- **Scalability**
- **Data Integrity and Storage**
- **Facility Throughput**
- **Clinical Handling**
- **Intermediate / Product Stability**
- **Raw Material Supply** (e.g. Adventitious agent Testing/Supply agreements/licensing)
**Accelerating your program development**

### Structure
- **Structured Development Program to meet Clinical Objectives**
  - Strategic development appropriate for clinical phase
  - Decrease time to pre-clinical & clinical studies
  - Focus on high priority areas

### Risk
- **Reduce the risk of an expensive, failed GMP Manufacture**
  - Financial Risk – Batch losses; Future investment
  - Reputational Risk – Company; Clinical uptake

### £
- **Reduce costs of the Development Program and GMP manufacture**
  - Decrease CoGs / Increase the probability of achieving the reimbursement price-point
  - Dendreon (Provenge) – Manufacturing CoGs up to 77% of $94,000 price tag.
  - TiGenix (Chondroselect) – Poor uptake in key markets – Reimbursement challenges
Design of Experiments (DoE) Philosophy

**One Factor At a Time (OFAT):**
- Poor coverage of experimental space
- May miss optimal solution

**Design of Experiments:**
- Good coverage of experimental space
- High efficiency designs
Theoretical Example of DoE

Knowledge Space

- Time in culture
- Vessel Type
- Detachment Agent
- Buffer Wash
- Surface Type
- Hold Time
- Feed frequency
- Wash Method
- Centrifugation Parameters

Choose factor ranges

Determination of relevant factors

Hold Time
Centrifugation Parameters
Wash Method

Adjust factor ranges accordingly

Optimisation

2-4h
200-500g, 10-15min
1-3 volumes

Setting Operation Bandwidth

Lock-down

3+/-0.5h
400g, 12 min
2+/-0.5 volumes

Design Space

Control Space
Logistics by Design

Creating a Framework to Support ATMP Commercialisation
Why do we need a Framework?

“Surely it’s just a case of picking up the phone and “voila”, next day delivery”

Unfortunately not - the logistics complexity surrounding ATMP manufacture and subsequent connection of final product to patient requires significant planning!

Logistics success will be influenced and impacted by several key stakeholders both internal and external to the therapy developer throughout the development lifecycle.

To be successful, the vision for a commercial logistics strategy needs to be planned early & have quality designed-in from the start.
Autologous CAR-T Immunotherapy – a simplified example of key shipments that may form part of the therapy’s value chain

<table>
<thead>
<tr>
<th>Category</th>
<th>Quantity/Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apheresis</td>
<td>3200 @ controlled ambient(?)</td>
</tr>
<tr>
<td>Product</td>
<td>6400 @ LQN Dryshipper</td>
</tr>
<tr>
<td>QC</td>
<td>320 shipments (x No. of different QC sites)</td>
</tr>
<tr>
<td>Raw Material</td>
<td>10 – 50 @ -80°C</td>
</tr>
<tr>
<td>Patient Samples</td>
<td>2 a year x 3200 = 6400</td>
</tr>
<tr>
<td></td>
<td>Track for 15 years, by year 15 you are doing</td>
</tr>
<tr>
<td></td>
<td>2 x 3200 x 15 = 96000 a year!!</td>
</tr>
</tbody>
</table>
Logistics - What could possibly go wrong?

STABLE THERMAL PACKAGING

SENSOR + COMMUNICATION  EMBEDDED PACKAGING

SECONDARY THERMAL PACKAGING for SITE
LOCAL TRANSPORT to BEDSIDE

DEDICATED THERMAL PACKAGING FLEET

AUTOMATED THERMAL PACKAGING RETURN

RETURN TO SENDER?
Logistics - What could possibly go wrong?

**Excursion Statistics**

<table>
<thead>
<tr>
<th>Type</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Alarm Threshold (°C)</td>
<td>16.0</td>
</tr>
<tr>
<td>Total Time Below</td>
<td>54h 20m 09s 08s</td>
</tr>
<tr>
<td>Longest Low Threshold Excursion Event</td>
<td>54h 20m 09s 08s</td>
</tr>
<tr>
<td>High Alarm Threshold (°C)</td>
<td>22.0</td>
</tr>
<tr>
<td>Total Time Above</td>
<td>50h 30m 06s 56s</td>
</tr>
<tr>
<td>Longest High Threshold Excursion Event</td>
<td>50h 30m 06s 56s</td>
</tr>
</tbody>
</table>

**Event Type**

<table>
<thead>
<tr>
<th>Event Type</th>
<th>Time</th>
<th>Duration in Minutes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decision Below Threshold</td>
<td>11-Jan-2018 01:23:04 GMT 0700</td>
<td>6280</td>
</tr>
<tr>
<td>Go into Below Threshold</td>
<td>15-Jan-2018 02:45:45 GMT 0700</td>
<td>675</td>
</tr>
</tbody>
</table>

Unique Challenges Posed by Cell and Gene Therapy Logistics and Packaging

- Manufacturing
- Site
- Patient
- Logistics provider
- Logistics vehicle
- Data integrator
- Qualified person
- To name a few...

**REAL TIME SYSTEMS INTEGRATIONS with PARTNERS**
Logistics - What could possibly go wrong?

AIRLINE RESTRICTIONS ON COMMUNICATION SYSTEMS

MANAGEMENT of TIME SENSITIVE SHIPMENTS

CLEANLINESS OF PACKAGING
The Key Elements

Logistics is more than just physical material movement.
When should I start planning?

As early as possible – Logistics should have lifecycle management plans similar to clinical and manufacturing development.
# Logistics by Design – Build in Quality from the Start

## Quality by Design

### Identify Design Space

- CPP
- CQA
- QTPP
- TTP

### Control Strategy

- CPP
- CQA
- QTPP
- TTP

### Process Validation & Monitoring

- CPP
- CQA
- QTPP
- TTP

## Logistics by Design

### Logistics Validation & Monitoring

- CLP
- CLA
- FTLP
- TLP

### Logistics by Design

- Target Logistics Profile
  - Overarching objectives of a commercial logistics strategy with respect to supporting business goals, supplying market needs, maintaining regulatory compliance and facilitating clinical adoption.

- Focused Target Logistics Profile
  - Prospective summary of the commercial logistics strategy traits that need to be achieved for all components of the value chain, to ensure successful delivery of product to patient whilst maintaining chain of custody and identity.

- Critical Logistics Attribute
  - A physical, temporal, informatic or operational property that needs to be within an appropriate limit, range, distribution or tracked and traced, to ensure the desired logistics strategy is fulfilled.

- Critical Logistics Parameter
  - A logistics parameter whose variability or failure would impact a critical logistics attribute and therefore should be monitored or controlled to ensure the desired logistics strategy is fulfilled.

- Identify Design Space
  - The design space or operating ranges for the CLPs are elucidated through practical assessment using supporting tools, such as Design of Experiments (DoE) or through the testing as part of logistics development activities.

- Control Strategy
  - A planned set of controls, derived from current logistics understanding that ensures service performance and quality. Controls may include parameters and attributes related to physical or informatic characteristics and include frequency of monitoring and control.

- Logistics Validation and Monitoring
  - A MAA/launch ready logistics system functional on a global footprint with regular performance review to support real time data driven decision making to further optimise the logistics undertaking.
Examples of Route Cause Failures

Identifying root cause failures of the planned logistics strategy

- Consignment Delivery
- Storage Requirements
- Staff Theatre Other
- Just in Time Off the shelf
- Holiday Unplanned event
- 196°C - 20°C
- 2 - 8°C Controlled Ambient
- 37°C Defined Window
- Intra-site Handling
- Controlled Temp Packs
- Physical Conditions
- Vibration High Impact (Drop)
- Size Contents
- Temperature Monitoring and Control
- Proximity to Product/Sample
- T-Flask Other
- Labelling
- Planning and Implementation
- Courier Single Provider Sub-contracted
- GMO Translation (Languages Required)
- Locations Tracking
- Real Time Tracking Systems Integration
- Manufacturing Site Data Management Provider
- Chain of Custody Management
- Tracking Devices
- Manufacturing Site
- Batch Documentation and Notification Points
- Electronic Courier / Shipment Organiser Notification Points
- Process Operation Staff
- Holiday Sickness Unplanned event
- Time Sensitive Shipments
- Competition / Restrictions Political Affairs
- Natural Disasters
- Xeno products

Route Cause Failures of a Logistics Strategy
Examples of Root Cause Failures

- **Physical Conditions**
  - Vibration
  - High Impact (Drop)
  - Size
  - Contents
  - Temperature

- **Monitoring and Control**
  - Temperature

- **Proximity to**
  - Product/Sample T-Flask

- **Labelling**
  - Other

- **Planning and Implementation**
  - Courier 3rd Party

- **GMO**

- **Translation**
  - (Languages Required)

- **Locations**
  - Time Sensitive Shipments

- **Product Shipment**
  - By Supplier
  - By End User
  - Patient

- **Clinical Acceptance or Administration Procedures**

- **Chain of Custody Management**

- **Shipper**

- **Broker**

- **Therapy Developer**

- **Start**

- **Locations**

- **Route**

- **Expire Notification**

- **Planning and Implementation**
  - Courier 
  - Single Provider 
  - Sub-contracted

- **Physicial Dimensions**
  - No. of product or sample units
  - Vial
  - T-Flask
  - Bag
  - Other

- **Contents**
  - GMO

- **Documentation**
  - Translation (Languages Required)

- **Data Loggers/Temp Probes**
  - Standard

- **Scope of Usage**
  - Probe Location and Type

- **Instruments**
  - Mini Incubator
  - Credo Cube
  - Dewar
  - Dedicated
  - Shared

- **Weight**

- **Preparation Time**

- **Internal**

- **Cleaning**

- **Packaging**
  - Return to Sender Procedure

- **Site Management**

- **Temperature Monitoring and Control**

- **Temp Control Mechanism**

- **Payload Shock**

- **Physical Conditions**
  - Xeno products
  - Vibration

- **Live Animals**

- **Other Cargo on same Shipment Route**

- **High Impact (Drop)**

- **Fixed**
  - Proximity to Product/Sample

- **Moving**

- **Temperature Monitoring and Control**

- **Shipping**
What’s the impact of manufacturing or clinical development teams deciding the product should be cryopreserved?
Case Study B: Mapping Shipping Lanes

What’s the impact on required shipping window / material shelf-life needs as a function of constrained elements within the shipping pathway?

*MC = Manufacturing Centre
### Case Study B: Mapping Shipping Lanes

<table>
<thead>
<tr>
<th>Destination</th>
<th>Original Collection Time (Local)</th>
<th>Original Scheduled Departure Time (Flight or Rail)</th>
<th>First Available &quot;Back-up&quot; Option</th>
<th>New Departure Time</th>
<th>Minimum Additional Shipment Time (h and min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>London</td>
<td>12:00</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Brussels</td>
<td>12:00</td>
<td>14:56</td>
<td>Later Flight - Same Day</td>
<td>16:56</td>
<td>2h 00 min</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>12:00</td>
<td>15:55</td>
<td>Later Flight - Same Day</td>
<td>20:30</td>
<td>4h 35 min</td>
</tr>
<tr>
<td>Paris</td>
<td>12:00</td>
<td>17:13</td>
<td>Later Flight - Same Day</td>
<td>19:13</td>
<td>2h 00 min</td>
</tr>
<tr>
<td>Prague</td>
<td>12:00</td>
<td>19:55</td>
<td>Later Flight - Next Day</td>
<td>13:45</td>
<td>17h 50 min</td>
</tr>
<tr>
<td>Warsaw</td>
<td>12:00</td>
<td>15:30</td>
<td>Later Flight - Same Day</td>
<td>20:00</td>
<td>4h 30 min</td>
</tr>
<tr>
<td>Copenhagen</td>
<td>12:00</td>
<td>20:35</td>
<td>Later Flight - Next Day</td>
<td>07:50</td>
<td>11h 15 min</td>
</tr>
<tr>
<td>Houston</td>
<td>12:00</td>
<td>16:25</td>
<td>Later Flight - Same Day</td>
<td>20:20</td>
<td>3h 55 min</td>
</tr>
<tr>
<td>Boston</td>
<td>12:00</td>
<td>19:15</td>
<td>Later Flight - Same Day</td>
<td>22:50</td>
<td>3h 35 min</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>12:00</td>
<td>16:55</td>
<td>Later Flight - Same Day</td>
<td>21:35</td>
<td>4h 40 min</td>
</tr>
<tr>
<td>Tokyo</td>
<td>12:00</td>
<td>01:55</td>
<td>Later Flight - Same Day</td>
<td>11:20</td>
<td>9h 25 min</td>
</tr>
<tr>
<td>Tel Aviv</td>
<td>12:00</td>
<td>07:35</td>
<td>Later Flight - Same Day</td>
<td>16:35</td>
<td>9h 00 min</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>London</td>
<td>12:00</td>
<td>13:30</td>
<td>N</td>
<td>1h 30 min</td>
<td>N/A</td>
</tr>
<tr>
<td>Brussels</td>
<td>12:00</td>
<td>19:05</td>
<td>Y</td>
<td>8h 05 min</td>
<td>14h 55 min</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>12:00</td>
<td>21:15</td>
<td>Y</td>
<td>10h 15 min</td>
<td>12h 45 min</td>
</tr>
<tr>
<td>Paris</td>
<td>12:00</td>
<td>20:30</td>
<td>Y</td>
<td>9h 30 min</td>
<td>13h 30 min</td>
</tr>
<tr>
<td>Prague</td>
<td>12:00 (+1) 01:25</td>
<td>Y</td>
<td>14h 25 min</td>
<td>8h 35 min</td>
<td>23h 00 min</td>
</tr>
<tr>
<td>Warsaw</td>
<td>12:00</td>
<td>21:50</td>
<td>Y</td>
<td>10h 50 min</td>
<td>12h 10 min</td>
</tr>
<tr>
<td>Copenhagen</td>
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<td>Y</td>
<td>15h 35 min</td>
<td>7h 25 min</td>
<td>23h 00 min</td>
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<tr>
<td>Houston</td>
<td>12:00</td>
<td>13:40</td>
<td>N</td>
<td>23h 40 min</td>
<td>N/A</td>
</tr>
<tr>
<td>Boston</td>
<td>12:00 (+1) 12:50</td>
<td>N</td>
<td>23h 50 min</td>
<td>N/A</td>
<td>23h 50 min</td>
</tr>
<tr>
<td>Los Angeles</td>
<td>12:00 (+1) 17:30</td>
<td>Y</td>
<td>25h 30 min</td>
<td>16h 30 min</td>
<td>42h 00 min</td>
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<tr>
<td>Tokyo</td>
<td>12:00 (+1) 11:55</td>
<td>N</td>
<td>35h 55 min</td>
<td>N/A</td>
<td>35h 55 min</td>
</tr>
<tr>
<td>Tel Aviv</td>
<td>12:00 (+1) 17:00</td>
<td>Y</td>
<td>35h 00 min</td>
<td>17h 00 min</td>
<td>52h 00 min</td>
</tr>
</tbody>
</table>
Cell and Gene Therapy Catapult is committed to ensuring high standards of research integrity and research best practice in the activities we carry out. We subscribe to the principles described in the UK concordat to support research integrity.