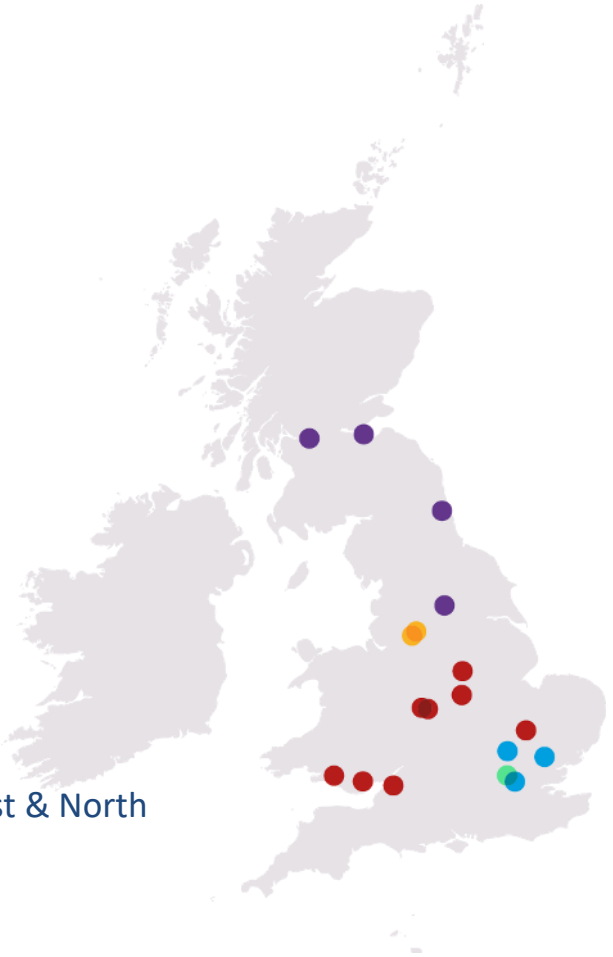
Advanced Therapy Treatment Centres

LONDON ADVANCED THERAPIES



Out of Specification ATMPs

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Funded by

INDUSTRIAL STRATEGY

UK Research and Innovation

Coordinated by

CATAPULT Cell and Gene Therapy

Out of Specification ATMPs

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Advanced Therapy Medicinal Products

An ATMP is a biological medicine.

Regulation (EC) No 1394/2007 **classified** ATMPs as:

- **Somatic Cell Therapy Medicinal Product (CTMP)**
- **Tissue Engineered Products (TEP)**
- **Gene Therapy Medicinal Product (GTMP)**

(or any combination of the 3)

Two Types of Gene Therapy

- **In Vivo**

  The vector is injected directly into a tissue where it is taken up by cells, or given intravenously.

  e.g. Adeno Associated Viruses

- **Ex Vivo**

  A sample of cells are taken and the vector is used to introduce the gene to the starting material cells

  e.g. CAR-T Therapy

How do we use ATMPs in Hospitals?

- Marketing Authorisation (MA)
- Investigational Medicinal Products (IMP)
- Unlicensed Medicines (ULM)

Medicines Regulation

Marketing Authorisation

Safety, Efficacy & Quality is assessed by the MHRA

- Submission of evidence gathered in preclinical, clinical trials and other technical data.
- Agreement of specification.
- QP Certification confirms MA specification has been met.

Medicines Regulation

Investigational Medicinal Products

- Sponsor submits a CTA.
- Incorporates an IMP Dossier which contains the product specification.
- QP certifies that the IMP is in line with specification contained in the IMPD.

Medicines Regulation

Unlicensed Medicines – MHRA Guidance Note 14 no need for MA if:

- The patient has a **special clinical need** (Cost, institutional need or convenience are not special clinical needs)
- Formulated in accordance with **specifications** of an authorised healthcare professional
- For use by healthcare professionals' **individual patients**
- Under **direct responsibility**

Hence the specification is agreed with the prescribing clinician.

Out of Specifications (OOS)

- Cellular/Tissue based Medicines are unique.
- On occasion, the finished product may not be in compliance with it’s specification.
- Specialist medicines, often irreplaceable, so depending on the degree of OOS, administration may be in patient's best interest.


Challenges
Regulatory
Governance (Liability)
Financial

Regulatory

- All medicines manufacture occurs in line with GMP (2003/94/EC)
- ATMP Regulation EC 1394/2007 references GMP
- Eudralex Volume IV Part 4: GMP for ATMPs

  - Exceptionally, physician can request release to avoid immediate patient hazard.

- UK still recognises European GMP (UK SI No775 2019 HMR Amendments for EU Exit)
- EMA Q&A (April 2019)
  - Manufacturer
    - QP Verification
    - Confirms GMP
    - Verify results against the expected specification of the MA
    - Notify competent authority

Eudralex Volume IV: Part GMP for ATMPs 11.5

- "Exceptionally, the administration of the cells/tissues that are contained in a cell/tissue based ATMP that is out of specification may be necessary for the patient. Where the administration of the product is necessary to avoid an immediate significant hazard to the patient and taking into account the alternative options for the patient and the consequences of not receiving the cells/tissues contained in the product, the supply of the product to the treating physician is justified."

- The manufacturer should provide the treating physician with its evaluation of the risks and notify the physician that the out of specification product is being supplied to the physician at his/her request. The confirmation of the treating physician to accept the product should be recorded by the manufacturer.

Specialist Pharmacy Service
www.sps.nhs.uk

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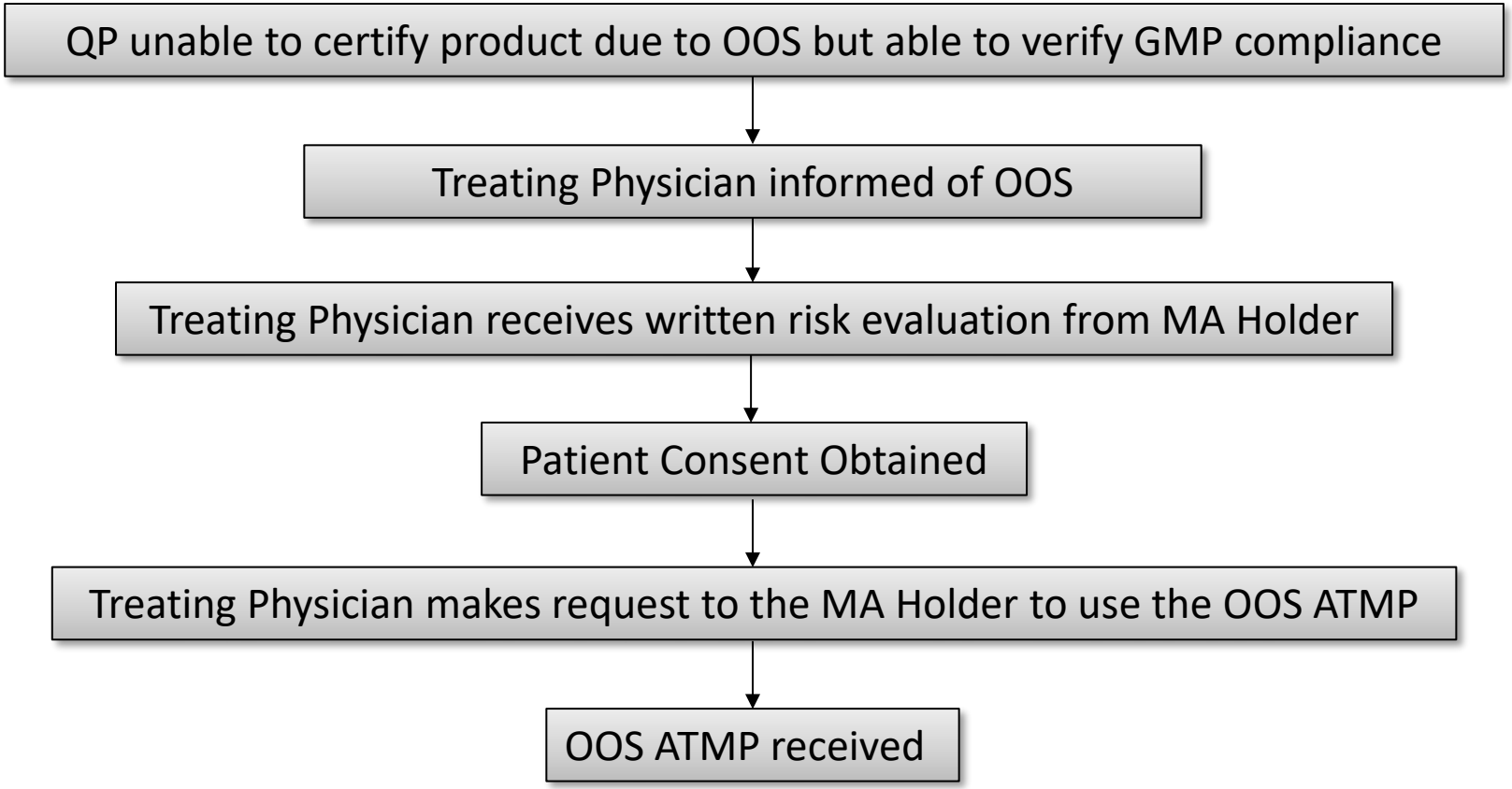
Minimum Legal Requirement in the event of an OOS Licensed ATMP



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Marketing Authorisation

Administration of OOS licensed ATMP is exceptional use of a medicine not in compliance with its MA.

Roles and Responsibilities - Manufacturer ✓

- MA Holder ✓
- Physician ✓

Liability Transfers to hospital then

- Organisational governance is needed ✗

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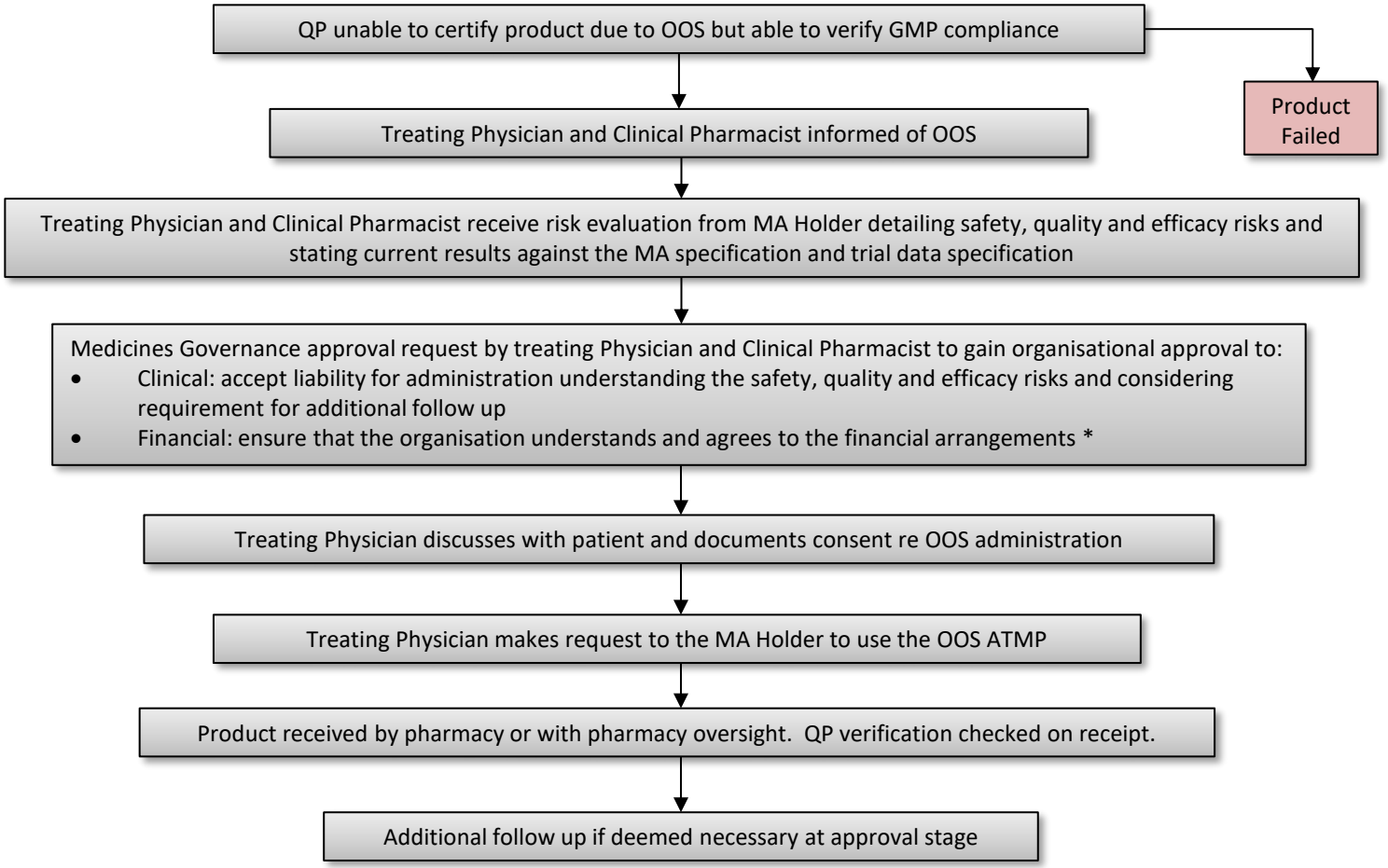
Recommendations for NHS Implementation



* see Financial and Commissioning Considerations

Investigational Medicinal Products

- Similar Principles as for MA products but in addition to remember that any clinical trial has:
  - Patient safety considerations
  - Data integrity considerations
- There are 2 options depending on the IMP:
  - Cryopreserved/long shelf life
  - Short shelf life

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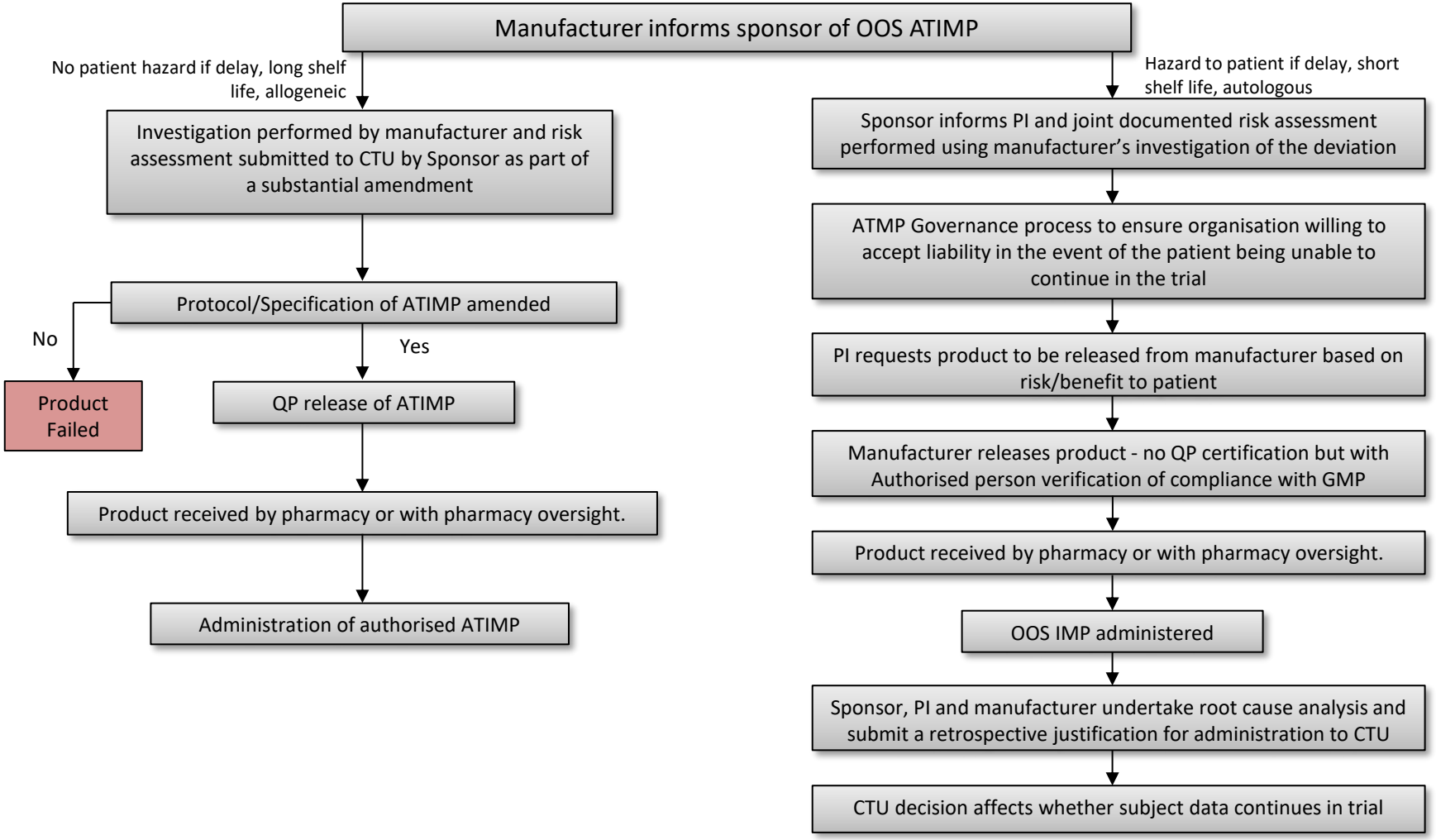
Recommended Hospital Process in the event of an OOS ATIMP



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Unlicensed Medicines

- In advance of manufacture, a clinician's patient has a special clinical need.
- No MA product suitable or available.
- Organisational governance approves the use and funding for an unlicensed special.

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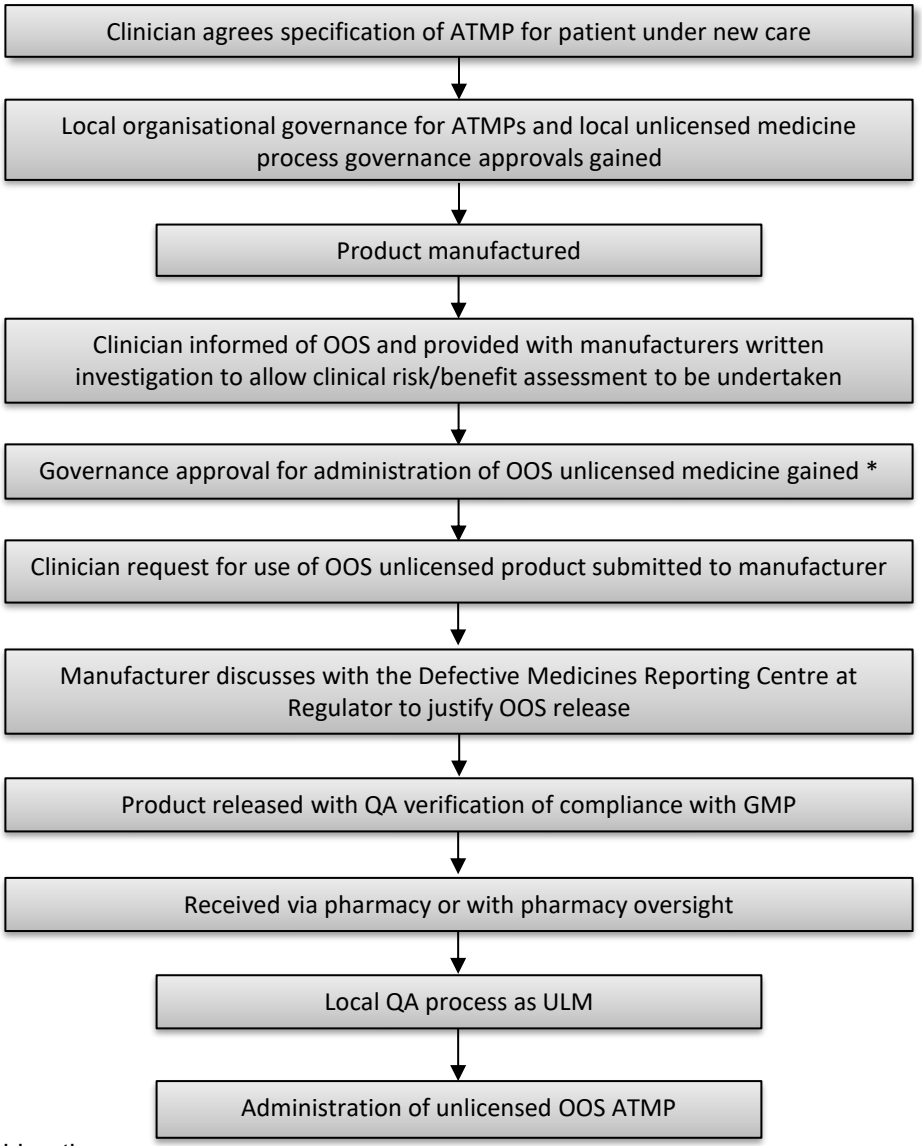
Recommended Hospital Process in the Event of an OOS Unlicensed ATMP



*see Financial and Commissioning Considerations

Financial Considerations

OOS Licensed Product

If commissioned via managed access Agreement (MAA) expectation is review after a period of time. Hence MA compliant product required.

Governance should consider:

- Medicine Cost
- Activity Costs (tariff)

OOS Licensed ATIMP

‘Tell and Do’ submission approved ✓

‘Do and Tell’ submission approved ✓

‘Do and Tell’ submission rejected ✘

Require Sponsor’s confirmation of funding and excess treatment costs as part of risk assessment/governance process.

OOS Unlicensed ATIMP

Governance process required to confirm funding.
Unlikely IFR funding or commissioned ULM would pay for OOS ULM

CAR-T Case Study

- MA Products commissioned for use by NHSE in December 2018.
- Understanding of Regulation of OOS and use evolved since then.
- OOS: Clinician informed
- Indication: DLBCL
  Patients in decline
- Funding a problem
  - Divergence in company approach
  - Commissioners approach

NHSE Facilitated …

- Subgroup of CAR-T Clinical Panel formed.
- Led by Tobias Menne with other CAR-T clinicians and 3 pharmacists from Pan UK Pharmacy Working Group for ATMPs.
- Formal Process requiring consensus.
- Individual cases assessed with a patient focus.
- Recognises that funding can be appropriate for some exceptional cases.

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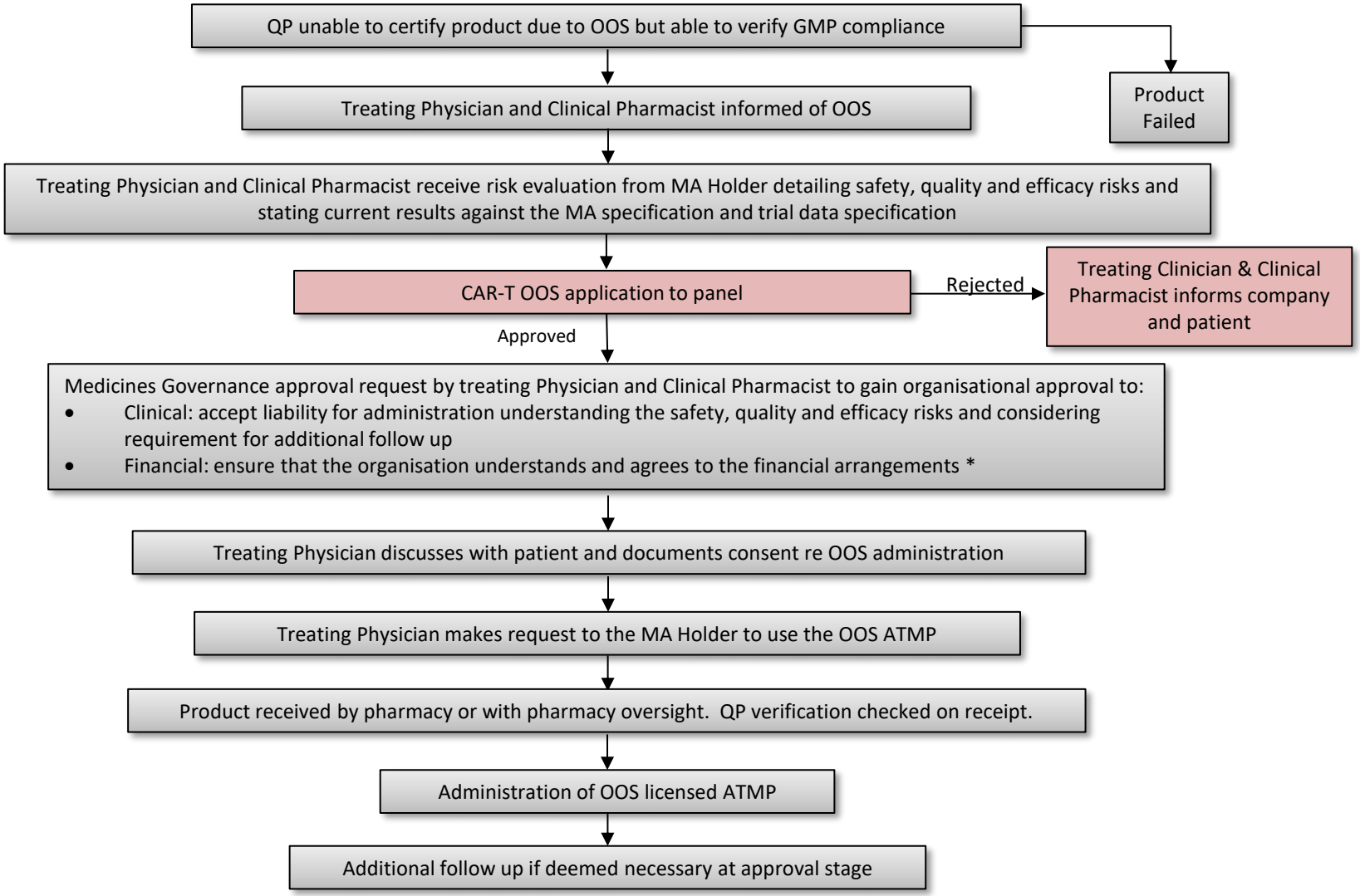
CAR-T OOS Process



* see Financial and Commissioning Considerations

OOS Summary

- Administration of OOS Cellular ATMP is permitted from a Regulatory Perspective.
- Organisational Governance understanding safety, efficacy and financial risks is required.
- Local ATMP Policies should include the process for governance of OOS ATMP.

Thank you for listening

Any questions

https://www.sps.nhs.uk/articles/out-of-specification-advanced-therapy-medicinal-products-guidance-for-healthcare-organisations/