

UK Market Access Considerations for the Cell Therapy Industry

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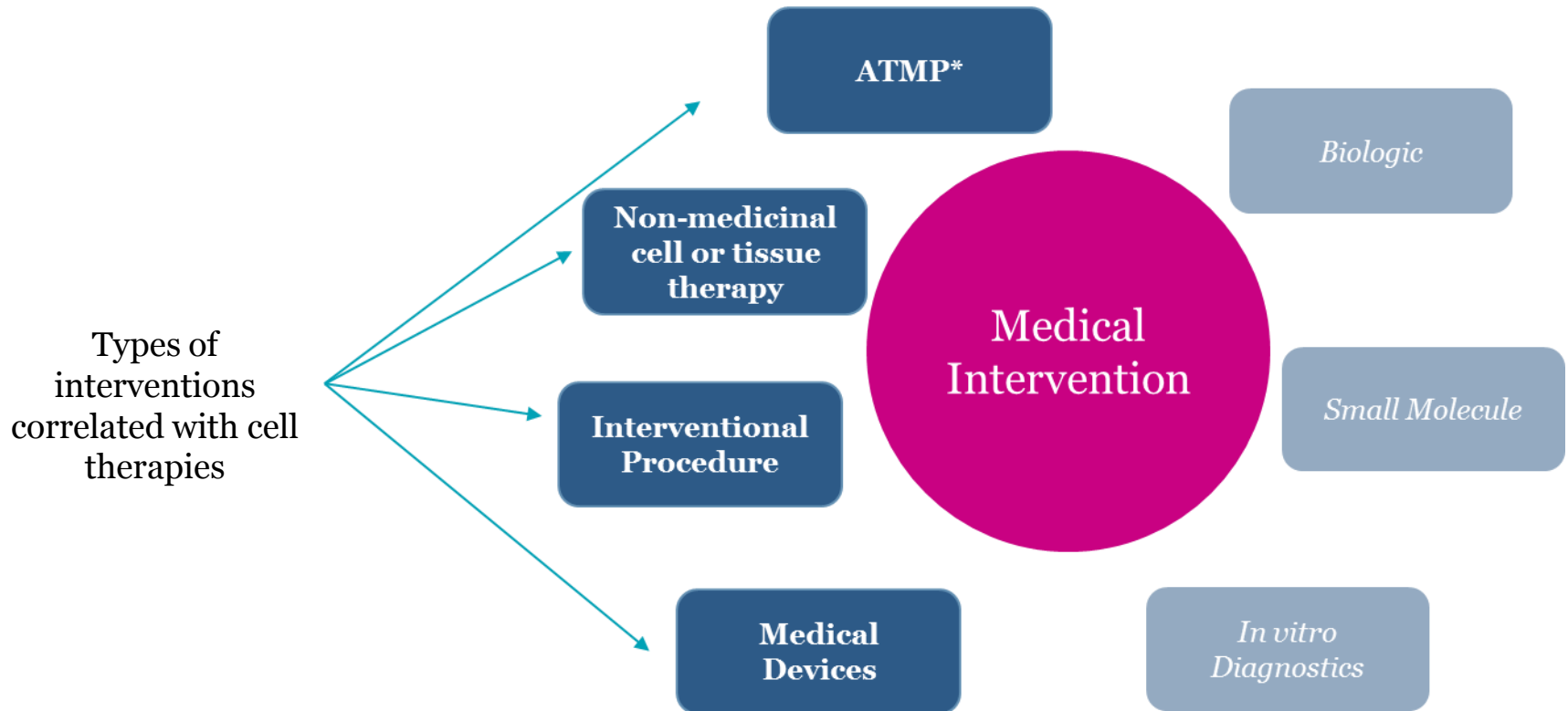
Health Economics & Market Access Lead

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With input from:

“The Evaluation and Commissioning sub-group of the Regenerative Medicine Expert Group”

The key medical interventions correlated with cell therapies include: ATMPs*, non-medicinal cell or tissue therapies, interventional procedures and medical devices



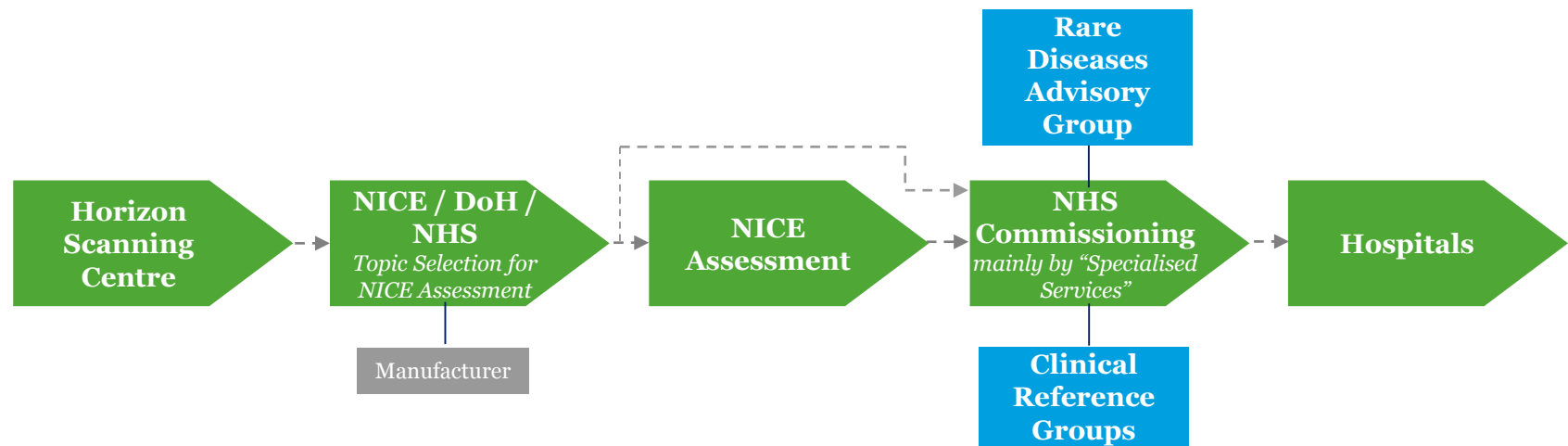
*Advanced Therapy Medicinal Product (licensed or not intended for licencing or unlikely to be licenced)

From a regulatory perspective applicable legislations vary across categories of medical interventions

Category	Definition	Applicable Legislation in UK	Licencing Route
Advanced Therapy Medicinal Product (ATMP) intending to gain market authorisation	Cell or tissue therapy used for medicinal purposes. More than minimally manipulated and / or intended for non-homologous use	ATMP Regulation and associated medicinal products legislation	European Medicines Agency (EMA) and National Competent Authorities (NCAs)
ATMP not intended for licencing or unlikely to be licenced (supplied under UK specials scheme)	As above but supplied to meet unmet clinical need, compassionate use provisions or for exploratory clinical research	As above for medicinal products but with some exemptions e.g. GMP still applicable but exempt from clinical trials and licencing requirements	EMA & NCAs for hospital exceptions, specials and compassionate use legislation
Non-medicinal cell or tissue therapy	Falls outside definition of medicinal product, not more than minimally manipulated and intended for homologous use	EU Tissue and Cells Directives	NCAs
Medical Device	Any device used in humans for diagnosis, prevention, monitoring, treatment and does not achieve its action by pharmacological, immunological or metabolic means. By definition, a human cell cannot be a medical device, but cell therapies may involve medical devices (e.g. for delivery)	EU Medical Devices Directives	Competent Authorities and Notified Bodies (for conformity assessments)

The route to NHS adoption for licensed cell therapies is described below

Top-level roadmap to market access for licensed cell therapies (England*)



Cell Therapy manufacturers should engage successfully with all above stakeholders in order to maximise therapy uptake.

*Equivalent to NICE assessments in Scotland are undertaken by the Scottish Medicines Consortium (SMC) and in Wales by the All Welsh Medicines Strategy Group (AWMSG); The Rare Diseases Advisory Group advises NHS England, NHS Scotland, NHS Wales, NHS Northern Ireland.

Two types of NICE assessments (TA and HSTE)* result in binding obligations for NHS commissioning: TA is employed for larger target populations

Out of ~200 new products launching p.a. only ~25% are assessed by TA or HSTE
Technology appraisals (~45 assessments p.a.)

Selection criteria	Elimination criteria	Prioritisation criteria
<ul style="list-style-type: none">▪ The technology is likely to result in significant:<ul style="list-style-type: none">▪ Health benefit▪ Impact on other health-related government policies (e.g. reduction in health inequalities)▪ NICE guidance is likely to add value because in its absence there is likely:<ul style="list-style-type: none">▪ Uncertainty over clinical and cost effectiveness▪ Variation in the use of the technology across the country	<ul style="list-style-type: none">• Unlicensed technologies (no plan to license)• Modification to an existing formulation or technology (e.g. me-too)• Population screening• Vaccination• HIV technology/therapy• Covered in existing guidance• Evidence lacking• Timing not close to launch• Does not address the key clinical question	<ul style="list-style-type: none">• Population• The larger the target population, the greater the prioritisation• Disease severity• Including: life expectancy; how far the individual is away from perfect health; health states that incur social stigma• Resource impact• Cost of implementation, facilities, staff requirements• Claimed therapeutic benefit over available NHS treatments

- TAs were originally applied to non-rare diseases, recently applied to diseases with three digit incidence
- The typical TA takes around 35 weeks; Multiple Technology Appraisals (MTAs) take around 14 months

Under the TA programme of NICE, incremental cost-effectiveness is the measure of value

$$\text{ICER} = \frac{\text{Cost B} - \text{Cost A}}{\text{QALY B} - \text{QALY A}}$$

- QALYs are the measure of clinical effectiveness

QALYs = Life expectancy (life years) x Quality of life (utility)

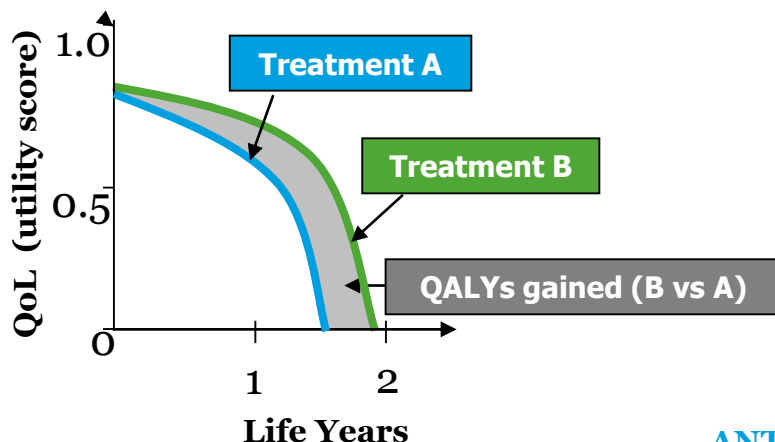
- Utility ranges from 0 (death) to 1 (full health)
- Utility determined by health-related quality of life (QoL) instruments; incorporation in clinical trials is key for market access

- Costs

- Direct (healthcare) and indirect (e.g. social care) costs

NICE ICER thresholds

- £20-30K/QALY; exact figure depends on:
 - The degree of certainty around the ICER
 - How adequately the change in QoL has been captured
 - How innovative the technology is
- End-of-life treatments for small populations (<7K) can exceed ICER threshold (up to a maximum threshold of £50K)
 - provided they extend life by ≥3 months



ANTICIPATED REFORMS

Incorporation of wider societal impact and disease burden considerations in current TA

HSTE* is appropriate for therapies for very rare diseases; however additional criteria should be fulfilled

HSTE (~3 assessments p.a.)

Selection Criteria:

- The technology is expected to be used exclusively in the context of a **highly specialised service**
- The target patient group for the technology **in its licensed indication is so small** that treatment will usually be **concentrated in very few centres in the NHS**
 - Originally defined as no more than 500 patients per annum
- Highly unlikely there is a **clinically meaningful alternative**
- The condition is **chronic and severely disabling**
- The technology **is likely to have a very high acquisition cost**
- The technology **has the potential for life long use**
- The target patient group is **distinct for clinical reasons** (e.g. not for genetic reasons alone)
- The **need for national commissioning is significant**
- Available data should **permit undertaking of assessment**

For licensed therapies that do not undergo TA or HSTE, other types of NICE guidance may be relevant to support adoption decisions by NHS commissioners

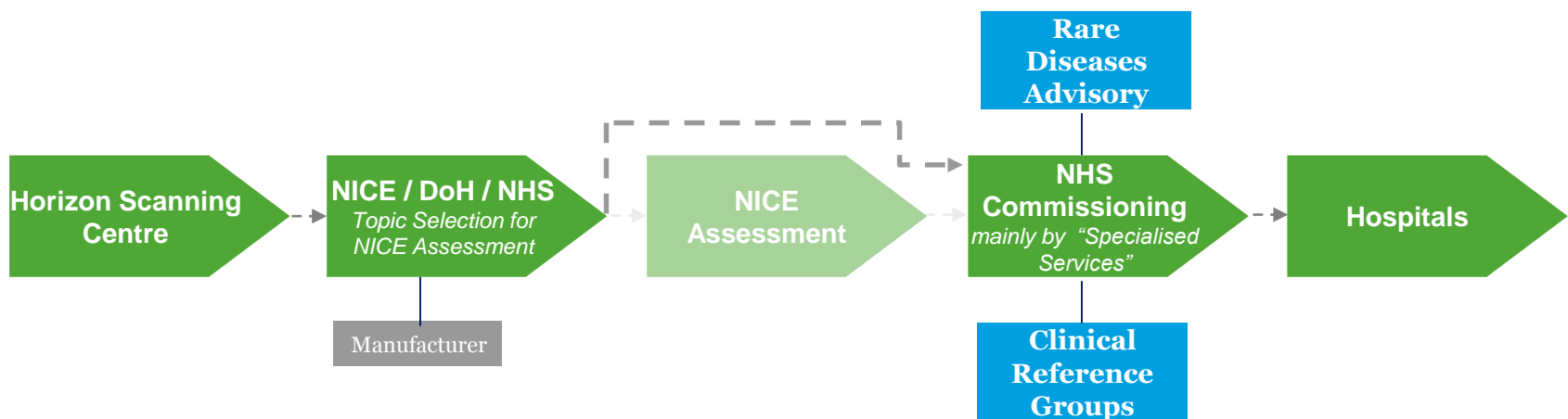
Alternatives

Category	Topic selection by:	Selection criteria	Methodology	Impact on NHS Commissioning
Technology appraisals (TA)	NICE/DoH	HTA selection criteria	Clinical and cost-effectiveness	Result in binding obligations for NHS commissioning
Highly Specialised Technologies Evaluation (HSTE)	NICE/DoH	HSTE selection criteria	Incremental QALYs and costs to the NHS and PSS, impact on budget for specialist commissioning, ethical considerations (for therapies with significant benefits for the patient and/or the healthcare system, development/ manufacturing costs may be accounted for)	
Medical Technologies Guidance (MedTech)	Notification by manufacturer	CE marked medical device; New or innovative modification of existing device; by definition, a human cell cannot be a medical device [viable or non viable] Note: ATMPs not eligible	Clinical effectiveness; cost consequence (e.g. cost-savings, cost-neutral)	Drives adoption of resource releasing technologies
Interventional Procedures Guidance (IPG)	Notification by manufacturer/ NHS clinicians	Therapies introduced into the body in a novel way, normally by an operator; a cell therapy may undergo both an IPG and a TA or HSTE ; Available data should permit undertaking of assessment	Safety and efficacy	Unlikely that a therapy requiring new IP would be commissioned in the NHS without IPG

For therapies without formal NICE assessment, NHS England will decide about their commissioning

- E.g. therapies with very small target population such as ADA-SCID* (~2 new patients p.a. in UK)
 - At first instance **Individual Funding Requests (by individual clinicians and hospitals) to NHS Commissioners** are likely to be required
 - After a number of these requests has been received (>20 nationally or >5 per region), NHS England would proceed with developing a centralised policy for commissioning the service

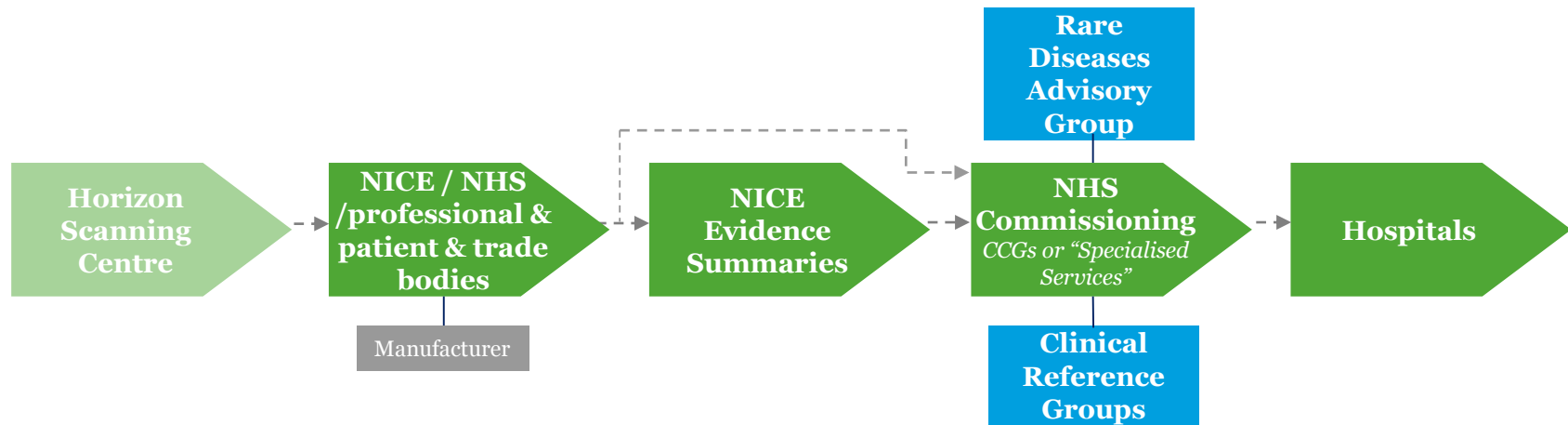
Top-level roadmap to market access for licensed ATMPs (England)



* Adenosine Deaminase Severe Combined Immunodeficiency

Not intended for licensing therapies do not undergo formal NICE assessment; NICE “Evidence Summaries” may be developed instead

Top-level roadmap to market access for unlicensed therapies (England)

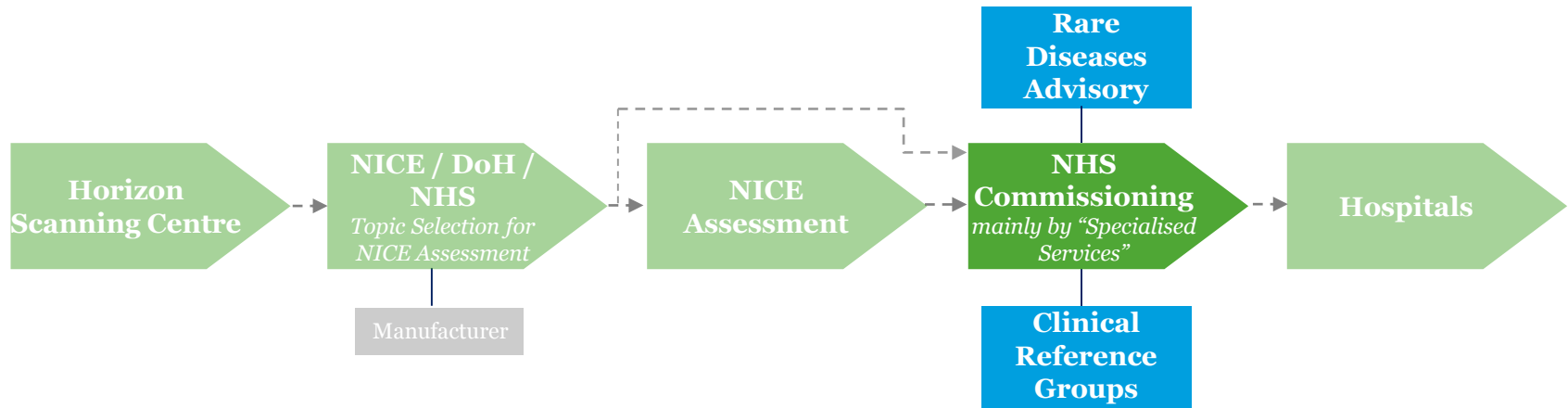


NICE “*Evidence Summaries*” are quality assured summaries of best available evidence that help NHS make informed decisions on commissioning new therapies which lack formal NICE guidance, including unlicensed/off-label therapies.

Whereas unlicensed therapies benefit from lower cost route-to-market, challenges for unlicensed therapies include:

- Weaker defensibility due to lack of data and market exclusivity
- Time-limited option, as it is theoretically contingent on the absence of an equivalent and available licensed product

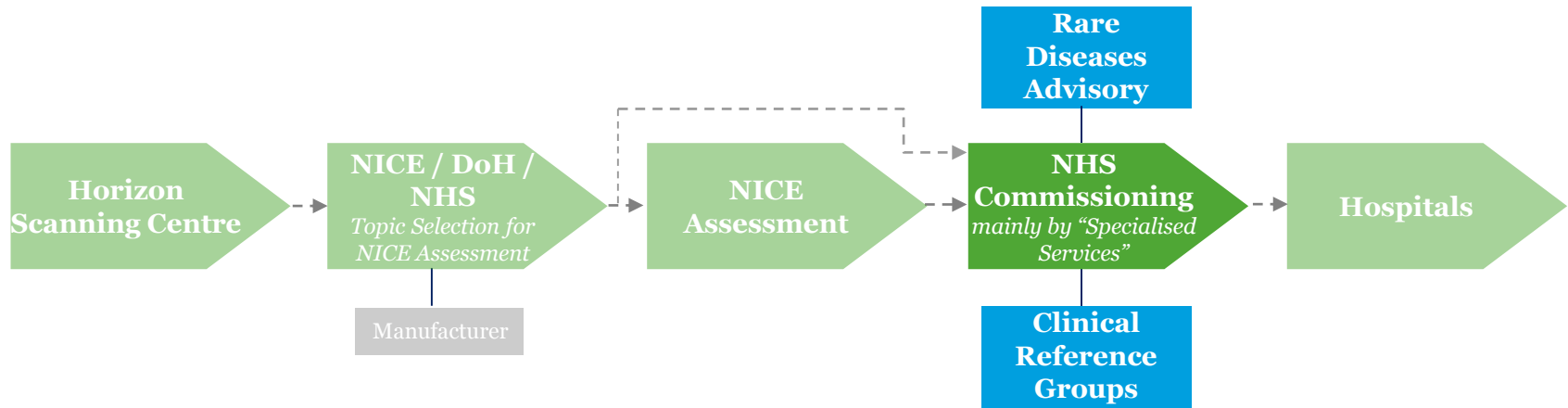
NHS commissioning of cell therapies in England is likely to involve the Specialised Services of the NHS



- Although many NHS services are commissioned by Clinical Commissioning Groups (CCGs / currently 211 across England), different arrangements apply for specialised services
- Specialised Services cover both licensed and unlicensed therapies ; four factors* determine whether NHS England commissions a therapy as a specialised service:
 - Size of target population
 - Cost of service or facility
 - Number of clinicians/hospitals able to provide the service or facility
 - The financial implications for CCGs if they were to arrange for provision of the service or facility individually
- There are 10 Area Teams that commission specialised services across England
 - Certain specialised services may be commissioned through overseas hospitals (e.g. proton beam therapy)

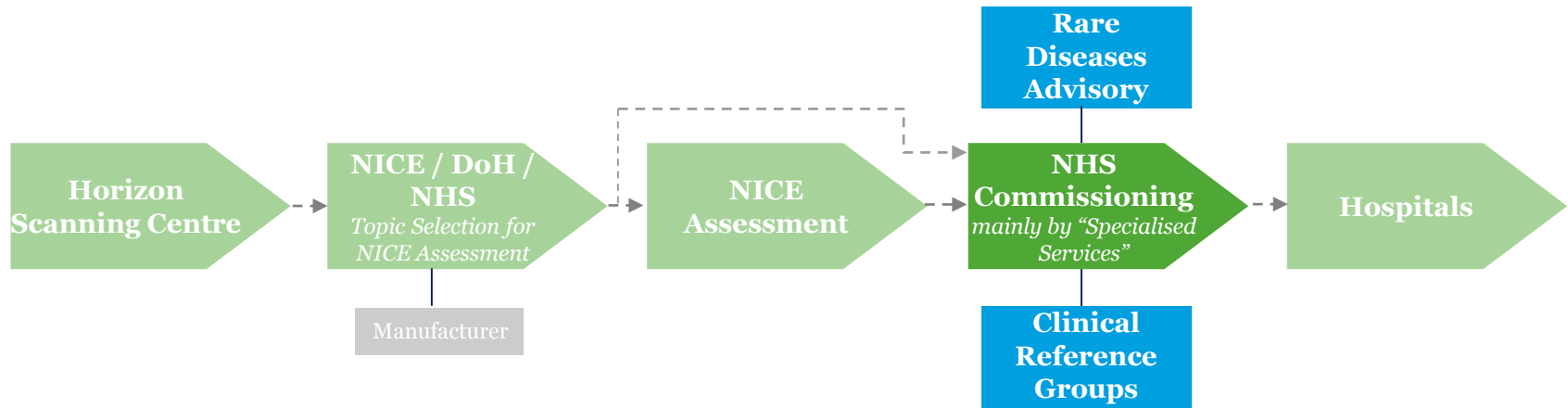
*Not all four factors need to be met e.g. chemotherapy commissioned through Specialised Services due to its high cost, despite the large number of patients involved

Clinical Reference Groups (CRGs) advice Specialised Services on commissioning decisions



- NHS England has launched 74 specialised services Clinical Reference Groups (CRGs)
- CRGs cover the full range of specialised services and are responsible for providing NHS England with clinical advice regarding these directly commissioned services
- The CRGs are made up of clinicians, commissioners, Public Health experts and patients and carers, and are responsible for the delivery of service specifications and commissioning policies

RDAG also advises NHS Specialised Services when therapies that target rare diseases* are involved



RARE DISEASES ADVISORY GROUP (RDAG)

- RDAG receives recommendations from Clinical Reference Groups (CRGs), and in addition will formulate its advice by calling on evidence from professional bodies and patient groups
- RDAG will make recommendations to NHS England, NHS Scotland, NHS Wales and NHS Northern Ireland on developing and implementing the strategy for rare diseases and highly specialised services
 - The Group will make recommendations to the NHS Clinical Priorities Advisory Group (CPAG) about how highly specialised services should be commissioned

Specialised Services develop Clinical Commissioning Policies and Policy statements

A. Clinical Commissioning Policy

- A document that defines access to a particular service/intervention for a cohort of patients:
 - Where a NICE TA is not published
 - If a NICE TA is published on the same topic, it will replace, or be incorporated into a commissioning policy

B. Clinical Commissioning Policy Statement

- An interim document that defines access to a particular service/intervention for a cohort of patients for use whilst a full commissioning policy is being developed or until a formal NICE TA has been published

Policies and Policy Statement are developed by CRGs and supported by:

- Specialised Services Clinical Effectiveness Team
- Public Health Lead supporting the relevant CRG/ Programmes of Care (POC)
- External expert support commissioned by NHS

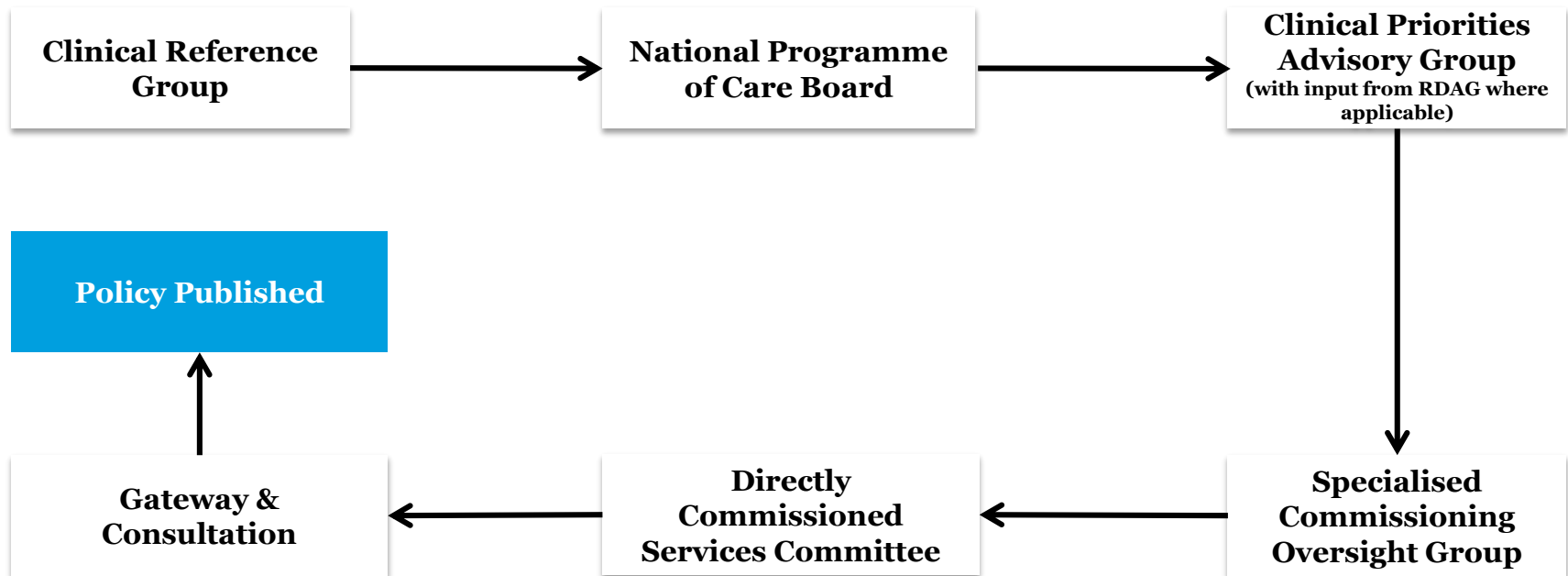
These are developed:

- If an intervention is not defined in a service specification or well established and its use in patients is likely to vary
- To define access to a specialised service for a cohort of patients based on the evidence of benefit and NHS value

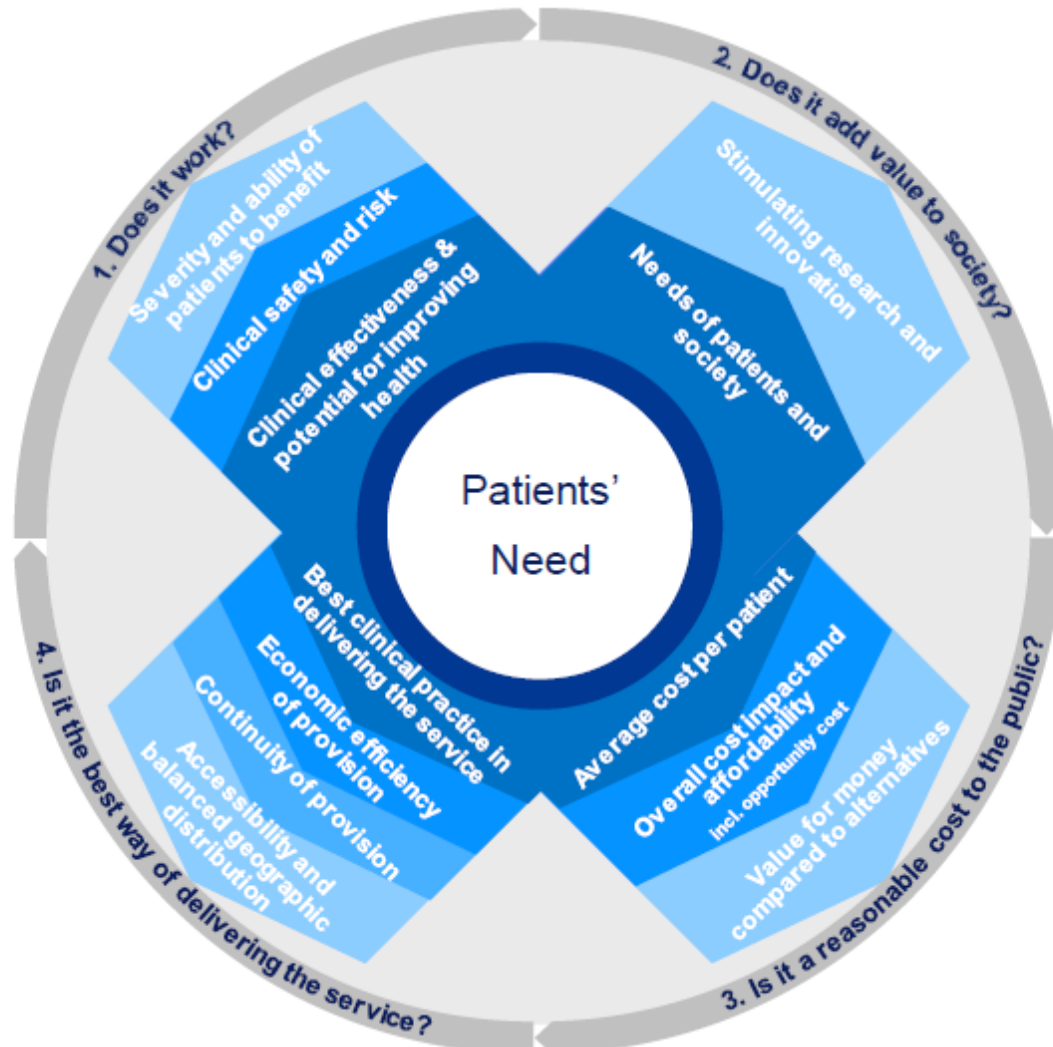
Topic selection involves the following routes:

- Clinical Reference Groups (CRGs)
- Individual Funding Request (IFR) reporting system and Local Area Teams
- Horizon scanning
- Partnership working with NICE

The governance process leading to a clinical commissioning policy is described below



Overview of the specialised services decision making framework applied to therapies that are not supported by NICE TA or HSTE



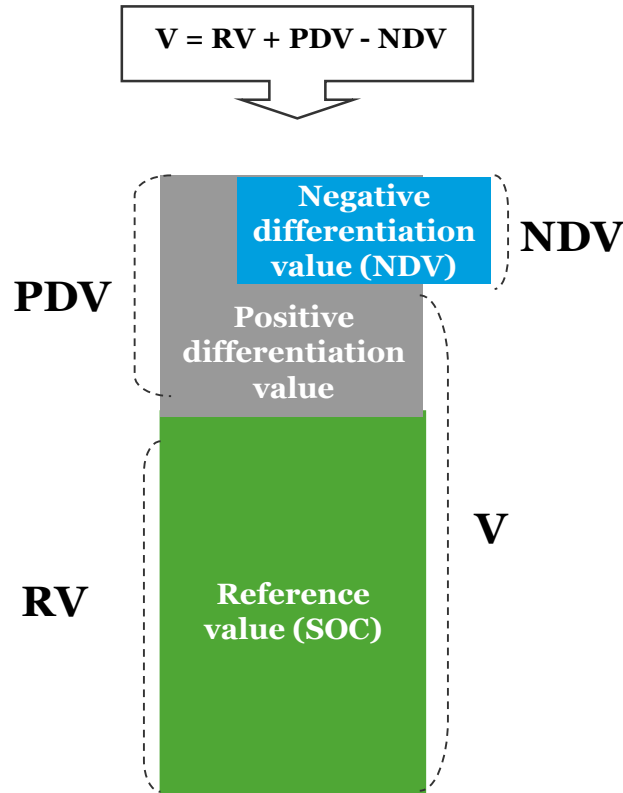
Key timelines for funding through Specialised Services

- The timelines for the Specialised Services decision making process differ whether the product has been assessed by NICE TA /HSTE or not
 - A. For a product that has been assessed by NICE TA or HSTE and receives a favourable recommendation:
 - It takes up to 90 days of the TA being published, for the Specialised Services governance process to be completed
 - B. For a product that has not been assessed by NICE TA or HSTE:
 - Once the CRG has made a recommendation/submitted a policy, it takes about 6 months for it to go through the governance process
- After Specialised Services decide that a product should be funded, there may be further delays between the decision and the actual adoption:
 - A. If the product is an in-year service development policy, this is funded immediately
 - B. If it is one that is to be considered in the annual prioritisation round, this will be funded from the beginning of the next financial year

In the UK, there is freedom for companies to determine their own list price; however PPRS imposes paybacks if profitability exceeds pre-specified limits; for reimbursement, additional considerations apply

- The Pharmaceutical Price Regulation Scheme (PPRS) has been renewed for a 5-year period (01/01/14-31/12/18)
 - it is the UK-wide voluntary price regulation scheme for branded, licensed Health Service medicines; it applies across the four nations of the UK
- UK have retained free pricing (within the restrictions of the scheme rules):
 - PPRS controls* profitability by setting limits on return on capital / sales for a company's portfolio as a whole rather than individual products; above these limits pay-backs are imposed
 - A pre-agreed level of growth rate is allowed for each year of the scheme
 - Price modulation across a company's portfolio is permitted as long as overall profitability limits are not exceeded
- The freedom that PPRS provides for companies to set their own list price rapidly at the time of launch and the flexibility it provides (e.g. through price modulation across a company's portfolio) encourages earlier therapy launch in UK than in traditional price-regulated markets
- UK list price is referenced by multiple countries: high UK list price boosts overseas price (25% of markets directly reference the UK price and 15% of markets reference indirectly)
 - Therefore UK is a market of strategic importance in a launch sequence
- However a PPRS-based list price does not necessarily secure NHS adoption; value-based assessments are involved in determining the reimbursed price level (see next slide)
- Where there is a differential between list and reimbursed price, this may be delivered via a company proposed patient access scheme. For simple discount schemes the reimbursed price is kept confidential so that international price referencing is not impacted

Value-based assessment relies on the quantification of the added-value that a new technology delivers over the SOC



Reference Value of Standard of Care (SOC)

- Comparative data against the SOC is required:
 - H2H comparative data demonstrating superiority or non-inferiority of Product X against the SOC is preferred
 - Indirect comparisons of high methodological standards (NMA) usually sufficient for non-inferiority claims

Differentiating Value e.g.

- Clinical effectiveness
- Economic impact: budget impact, cost-minimization, cost-effectiveness, cost-utility

Value (V)

- For a given indication “V” varies depending on the intervention’s positioning in the treatment algorithm & the target patient profile

Uncertainties over budget impact, clinical and cost-effectiveness necessitate innovative pricing agreements

Payers are increasingly resistant to budget uncertainties

- Uncertainties arise from:
 - Not well established clinical and cost effectiveness profiles at launch
 - Variation in individual patient needs for dosing and length of treatment
- These have lead to numerous innovative pricing agreements (e.g. “patient access schemes” in the UK)
 - Financially based
 - Manufacturer offers discounts or rebates
 - Manufacturer changes price (change may be kept confidential)
 - Outcomes - based e.g.
 - If value is proven, price can increase
 - If value is not proven, price will decrease
 - Risk-sharing e.g.
 - Velcade in progressive multiple myeloma: manufacturer rebates the full cost of Velcade for people who, after a maximum of four cycles of treatment, have less than a partial response (defined as reduction of serum M protein by $\leq 50\%$) - *NICE TA129*



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Technology Strategy Board

Driving Innovation

