Advanced Therapy Treatment Centres

Northern Alliance Advanced Therapies Treatment Centre

Coordinated by CATAPULT Cell and Gene Therapy

Advanced Therapy Medicinal Products

A guide to preparing for Health Technology Assessment in the United Kingdom | June 2021

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Chiesi

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The ATTC network programme is a UK system of Advanced Therapy Treatment Centres (ATTC) operating within the NHS framework and coordinated by the Cell and Gene Therapy Catapult (CGT Catapult) to address the complex challenges of bringing advanced therapy medicinal products (ATMPs) to patients through three regional centres, one of which is the Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC). The network is supported by the Industrial Challenge Strategy Fund delivered by UK Research and Innovation

J Horscroft[1], A Chapman[1], A Barnes[1], D Gladwell[1], C Bojke[2], G Amatt[3], J De-Almeida[3], E Morrison[4], C Van Niekerk[4], L Wotherspoon[4], G Rutherford[4], J Jorgensen[5], P Kefalas[5]

[1] BresMed Health Solutions, UK
[2] University of Leeds, UK
[3] Chiesi Farmaceutici S.p.A., Italy
[4] Northern Alliance Advanced Therapies Treatment Centre, UK
[5] Cell and Gene Therapy Catapult, UK

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Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ATMP	Advanced Therapy Medicinal Product
BIA	Budget impact analysis
CAR	Chimeric antigen receptor
CDF	Cancer Drugs Fund
CED	Coverage with evidence development
CHMP	Committee for Medicinal Products for Human Use
CRG	Clinical Reference Group
EAMS	Early access to medicines scheme
EMA	European Medicines Agency
EoL	End of LIfe
EQ-5D	EuroQoL 5 Dimension questionnaire
ERG	Evidence Review Group
HRA	Health Research Authority
HRQL	Health-related quality of life
HST	Highly Specialised Technologies
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
ILAP	Innovative Licensing and Access Procedure
MEA	Managed Entry Agreement
MHRA	Medicines and Healthcare products Regulatory Agency
NA-ATTC	Northern Alliance Advanced Therapies Treatment Centre
NDC	New Drugs Committee
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
OMA	Office for Market Access
PACE	Patient and Clinician Engagement
PIM	Promising innovative medicine
PSS	Personal social services
QALY	Quality-adjusted life years
RMEG	Regenerative Medicine Expert Group
SMC	Scottish Medicines Consortium
SME	Small and medium-sized enterprise
STA	Single technology appraisal
WP	Work package

1. Introduction to the Northern Alliance and Work Package 4

The Northern Alliance

The Northern Alliance Advanced Therapies Treatment Centre (NA-ATTC) is an Innovate UK funded project with a large consortium of industry, NHS and academic organisations led by The Newcastle upon Tyne Hospitals NHS Foundation Trust and the Scottish National Blood Transfusion Service. The purpose of the centre is to develop the systems and infrastructure to support the delivery of cell and gene therapies, with the aim of increasing patient access to Advanced Therapy Medicinal Products (ATMPs) on a national level.

The activities required to achieve NA-ATTC's wide-ranging remit are divided into a series of work packages (WPs). Each WP has its own focus within an overall integrated project structure and is led by experts in the respective field, full information can be found here **https://www.theattcnetwork.co.uk/centres/northern-alliance/activity**. WP 4, headed up by Greg Amatt, Director of Special Care and Rare Diseases, Chiesi Ltd, and Ewan Morrison, Director of Pharmacy, NHS National Services Scotland, has a focus on Infrastructure, Reimbursement and Outcomes for ATMPs.

This guide

One of WP 4's main objectives is to support ATMP developers and NHS Trusts and Boards accelerate the adoption of these innovative medicines by providing guidance on regulatory, health economy and commissioning processes and pathways.
This guide to preparing for Health Technology Assessment (HTA) in the UK has been developed with expert guidance from senior health economists and ATMP developers to help ensure that submissions to HTA bodies are robust and meet adoption requirements.

Expert guidance is provided in relation to:

- Best practice for developers regarding quality of life approaches for ATMPs - this guide identifies possible quality of life approaches and offers recommendations.
- Production of a health economic framework for ATMPs – this will assist ATMP developers to identify considerations for health economic analysis as part of the data submission to HTA bodies.
- Production of a guidance note for developers on how to ensure their product is identified in horizon scanning processes by HTA bodies.

2. Background

The fundamental issue facing all healthcare providers is that there are unlimited healthcare needs and wants across the population they serve and only a fixed budget with which to address those needs.

Ultimately there is no solution to this issue – even if budgets were to substantially increase we could simply never meet all wants and needs. In recognition of this unresolvable issue, HTAs have increasingly incorporated a health economics element or economic evaluation to assess whether technologies represent good value and budget impact analysis (BIA) to assess whether they are affordable. This assists healthcare providers to maximise the health outcomes given their limited resources. As funding for ATMPs represents a use of these resources then they should be subject to the same considerations as other technologies and service changes.

Although different countries adopt different methods for economic evaluation, there is a broad consensus on the underlying theoretical framework on which all nation-specific methods are based. For example, it is largely recognised that healthcare systems undertake a huge variety of activities which may all have outcomes measured in different metrics – so how can we compare outcomes? Furthermore, it is also recognised that ultimately what matters most is the benefit to patients themselves and their quality of life rather than a more narrow clinical end-point. This has led to the emergence of a generic measure of a health technologies benefit capturing the impact on a patient's health related quality of life (HRQL), conceptually measured by quality-adjusted life years (QALYs) and captured in real-life by using standard generic instruments like the self-reported EuroQoL 5 Dimension questionnaire (EQ-5D). There are many issues with the QALY concept but it has emerged as a pragmatic, if not perfect, instrument of measuring outcomes across the full range of healthcare activity. Recognising this reimbursement requirement by demonstrating the value of the technology in QALYs is critical to understanding potential value and evidence development requirements right through the technology development timelines. This guide will therefore cover the principles around health economic review (Section 8) and provide reference to the key country-specific frameworks (Section 9).

Although there is a standard generic framework that in principle could be used to assess any potential use of scarce resources, assessing ATMPs may bring special challenges which are not yet fully recognised or adequately addressed in national frameworks which are constantly evolving (discussed in Section 7). It is also important to recognise that no system uses economic evaluation as the sole decision making instrument, but rather as one input into a complex decision making process. If specific elements of value are not captured and quantified within the economic evaluation then they may be argued alongside the economic evaluation, often in a less structured, quantified or formal manner. For example, the current framework assesses technology value over a time period in which the treatment is expected to have a different impact to other currently available treatments but within a static landscape (i.e. it assumes no other technological changes). Potentially, adoption of an ATMP could increase the likelihood of further improvements in care that are dependent on that ATMP being utilised to treat patients. Currently there is no scope for including the 'innovative value' within economic evaluation. It is a problem that exists for current evaluations but in a world of 'me too' evaluations the omitted value is less likely to be an issue. The National Institute for Health and Care Excellence (NICE) has declared that the existing framework is fit for purpose[1], though many have the opinion that it can, and should be, re-evaluated. At the time of publication the NICE process is being reviewed.

2. Background

Other issues that may be especially pertinent to the assessment of ATMPs revolve around the increased uncertainty regarding the evaluation of these new medicines due to a weaker evidence base. Although the NICE framework is very prescriptive on the need and methods to describe and quantify uncertainty, there is a lack of clarity on how uncertainty should be formally incorporated into an adoption decision, possibly due to a lack of consensus in the academic health economic community. More recent developments in the methodology of accommodating uncertainty show great promise[2] but are yet to influence the reference case framework. So this is again an issue about the degree of suitability of the existing methods for assessing ATMPs. Thus to maximise the potential for ATMPs it is not always sufficient to solely follow the reference case modelling methods but to be fully aware of the limitations in the evidence base and the likely consequences and what strategies might be put in place to mitigate those issues. For example, if a technology is associated with high levels of uncertainty, then possible solutions may require a commitment to longer term follow-up of data and risk management. A method that indicates that companies are willing to share the risk with the NHS not only pools the risk, but sends a strong signal that the company believes in its product.

It is also likely to be the case that the evidence base will more heavily rely on non-randomised controlled trial data and there may be greater need to explore the methods we need to use in order to avoid biases from using observational data.

Overall, the objectives of this guide are to:

- Identify the best practice in economic evaluation as it pertains to ATMPs.
- Identify the limitations in the current methodology that are particularly important for the development of ATMPs and the steps that can be taken to mitigate against those limitations.

It is also our intention to encourage the need to incorporate the development of the economic evaluation as early as possible in product development. Development and application of early stage economic modelling is a wonderful means of identifying exactly what the evidence needs are and can be hugely influential in determining the structure of trials, observational data collection and elicitation of expert opinion where no evidence exists.

3. An overview of the Regenerative Medicine Expert Group subgroup for evaluation and commissioning

Why was a parliamentary expert group formed?

In 2013 the House of Lords Science and Technology Committee produced a report on its inquiry into Regenerative Medicine. The report announced that there should be the convening of a Regenerative Medicine Expert Group (RMEG) to *"develop an NHS regenerative medicine strategy so that the NHS is fully prepared to deliver these innovate treatments, and also assess the effect of regulation on the development of Regenerative Medicine in the UK".*[3]

The RMEG formed in 2014 and comprised pan-UK representatives from NICE, NHS England, regenerative medicine companies, clinicians, patient organisations, academics and the Cell and Gene Therapy Catapult. This group was tasked with developing an NHS regenerative medicine readiness strategy and assessing the effect of regulation on the development of regenerative medicines within the UK. Three sub-groups were formed to analyse and gather evidence in the following areas; regulation and licensing; evaluation and commissioning; and delivery.

Has this determined whether there are existing processes in the UK that are robust enough to review ATMPs?

In this guide, focus has been drawn to the RMEG's Evaluation and Commission sub-group's findings and recommendations[4]; this sub-group stated that NICE has limited experience of appraising regenerative medicines and its recommendations fell into three areas: Evaluation, Commissioning and Advice and Guidance.

3. An overview of the Regenerative Medicine Expert Group subgroup for evaluation and commissioning

Evaluation

The sub-group endorsed the proposal that NICE should consider the findings from one or more 'mock' technology appraisals and whether changes to its methods and/or processes are required. The mock technology appraisals should look at exemplar regenerative medicine products, for example, T-Cell therapies, and any appraisal should include expert advice.

The sub-group also stated that there are several barriers to the adoption of products into the NHS:

- *"High acquisition costs because of the nature of the starting materials, the complex manufacturing process and the clinical development pathway.*
- *Insufficient pathway and support infrastructure for healthcare providers to use these novel, unfamiliar and relatively expensive products.*
- *Uncertainties in estimating long-term clinical effectiveness by extrapolation of data from short-term clinical trials.*
- *The different approaches required in autologous or allogeneic use and different issues pertaining to base material, for example, human embryonic stem cells."* [4]

Commissioning

There are significant challenges in generating the quality of evidence required for robust assessment of regenerative medicines, long-term impacts. Due to the limited data available around regenerative medicines' longer-term effectiveness can only be extrapolated from shorter-term clinical trial data based on professional judgement. In addition, some regenerative medicine treatments may receive marketing authorisation but are not eligible for NICE evaluation due to very small patient populations. If commissioned by NHS England they fall within the remit of specialised services. The Clinical Reference Groups (CRGs) develop these policies and currently cover various medical specialties. However, there is no CRG for regenerative medicine.

With these points in mind the sub-group made the following recommendations:

- *"An innovative business model is developed between industry, government and the NHS, to support the early adoption of regenerative medicines in the NHS.*
- *NHS England's cross-CRGs for regenerative medicine be maintained; and, potentially, further developed into a formal 'CRG for regenerative medicine' as new products are identified for consideration. This CRG should include clinicians covering an appropriate range of specialties and experiences in regenerative medicine in order to provide more specific expertise, insight and advice to other CRGs."* [4]

Advice and Guidance

When the sub-group made it's recommendations, the cost of scientific advice from NICE, in conjunction with the Medicines and Healthcare products Regulatory Agency (MHRA), to aid the design of clinical trials ranges from £30,000 to £70,000.[4] To date, most of NICE's clients have been pharmaceutical and biopharmaceutical companies. This cost, however, is vastly out of reach for some regenerative medicine developers.

Taking this into consideration the sub-group recommended:

- *"NICE develops a scientific advice product, focused on the needs of SMEs developing regenerative medicines, and explores options for supporting access to this.*
- *NICE and NHS England, together with the Cell Therapy Catapult, should jointly develop and provide a bespoke seminar on evaluation methods and on how best to develop a value proposition for regenerative medicines."*[4]

RMEG's recommendations included above are from its report: 'Building on our own potential: a UK pathway for regenerative medicine' 2015. The full report can be accessed **here.**[4]

3. An overview of the Regenerative Medicine Expert Group subgroup for evaluation and commissioning

Sub-group outputs and conclusions

Some regenerative medicine treatments are well established in certain disciplines such as leukaemia and anaemia. However, the report published by RMEG focused on the type of regenerative medicine technology that is still very much emerging. The UK has many strengths including its academic centres, the NHS and industry; but there is considerable additional regenerative medicine investment in the USA and Japan. Also, Japan has introduced a Regenerative Medicine Law, aimed at accelerating the clinical trials process through a form of early conditional licensing.[4] The main output which followed the RMEG report 'Building on our own potential: a UK pathway for regenerative medicine'[4] was the mock Health Technology Assessment undertaken by NICE to assess whether changes to its methods and processes are needed.

'Mock' Health Technology Assessment (HTA)

'The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal' was conducted by experts from the University of York in 2015.

The research included reviews to identify issues, analysis methods and conceptual differences and the relevance of alternative decision frameworks, alongside the development of an exemplar case study of chimeric antigen receptor (CAR) T-cell therapy for treating acute lymphoblastic leukaemia.

In summary, the overall findings[5] of the exercise were that:

- *"The NICE appraisal methods and decision framework are applicable to regenerative medicines and cell therapies.*
- *Quantifying and presenting clinical outcome and decision uncertainty was key to the Expert Panel consideration of the hypothetical example products.*
- *Where there is a combination of great uncertainty but potentially very substantial patient benefits, innovative payment methodologies need to be developed to manage and share risk to facilitate timely patient access while the evidence is immature.*
- *The discounting rate applied to costs and benefits was found to have a very significant impact on analyses of these types of technologies."*[6]

The paper presenting the overview of the project designed to test whether the NICE HTA methods and processes are fit for purpose for regenerative medicines and cell therapies can be **found here**.

The full 'Mock' HTA can be obtained via the **following link**.

4. Considerations for clinical study design of ATMPs

Introduction

When designing clinical trials for ATMPs, it is essential to keep regulatory process requirements in mind. However, for ATMP manufacturers seeking market access in the UK, an equally critical consideration is HTA. This requires careful planning and consideration. Regulatory authorities aim to weigh up the risk/benefit ratio of a product but HTA agencies are concerned not only with the existence of an incremental health benefit, but also its magnitude, in order to robustly assess product value. This results in a slightly different set of evidence requirements at HTA in comparison with the regulatory stage.

Consequently, it is important to ensure that: i) the pivotal trial collects the most appropriate information for both regulatory and HTA audiences and ii) manufacturers recognise and identify the evidence gaps that the trial is not able to address. This will enable them to initiate robust evidence generation activities that address evidence gaps which cannot be filled as part of the clinical trial. Even the most robustly designed clinical trial cannot address all the uncertainty surrounding the comparative effectiveness and safety of a product in the real world. However, early recognition of such evidence gaps can allow for robust supplementary evidence generation to be initiated in parallel to the clinical trial to aim for an optimal evidence package for regulatory and HTA decision making.

For ATMPs this is particularly pertinent for several reasons:

1. Randomised head-to-head comparisons are often unfeasible or unethical because ATMPs frequently target rare conditions and are expected to confer a large comparative benefit.
2. This expectation of a large comparative benefit can also lead to the desire for accelerated access, which increases the level of uncertainty (particularly surrounding long-term outcomes) at the time of assessment.
3. ATMPs are often developed for rare diseases, where small sample sizes and heterogeneous populations create concerns around generalisability to real-world patient populations.
4. Relationships between measurable trial endpoints and patient-relevant outcomes are under-studied and poorly understood, because the mechanisms of action of ATMPs are often novel and knowledge about disease pathophysiology may be lacking.

Given these considerations, ATMP manufacturers are strongly advised to begin strategic planning, with both regulatory and HTA challenges, in mind as early as possible. The optimal timing of this strategic planning is difficult to pinpoint, as many clinical programmes for ATMPs do not follow the standard progression through Phases 1, 2 and 3. However, it is preferable that this is completed before the pivotal clinical trial is designed. This allows anticipated challenges at regulatory and HTA stages to be mitigated through adjustments to the trial design. Manufacturers are likely to face seven key challenges when demonstrating the value of ATMPs to HTA agencies. These challenges are detailed below and a framework is outlined for proactively overcoming these challenges.

4. Considerations for clinical study design of ATMPs

Value demonstration for ATMPs

Challenge 1: Uncertain treatment pathways

Although several ATMPs have been developed for more common oncological conditions, many others are targeted at treating rare diseases, where pre-existing disease-modifying treatments are often lacking. In these cases, current treatment is often symptomatic, variable, and unknown. UK HTA agencies will not accept the notion that "there is no comparator" and manufacturers will be expected to not only identify the current standard of care in UK clinical practice (which may differ between England, Scotland, Wales and Northern Ireland), but also to make efforts to establish an estimate of the relative effectiveness of the new product against these comparators (see Challenge 5).

To address this uncertainty, ATMP manufacturers can help to galvanise clinical opinion leaders and patient groups via advisory boards, Delphi panels and other mechanisms. Doing so can unveil a consensus on current approach to treatment where it exists, but can also help to shape it where it does not and encourage the development of clinical guidelines, particularly if the ATMP is the first targeted treatment for a condition. Improving understanding of who is treated and how they are treated can also illuminate the burden of disease (and burden of existing treatment), which can help to define the value story for the new product.

Challenge 2: Poorly defined populations

Another common challenge for ATMPs targeted at rare diseases is the definition of the patient population in practice. Where clear diagnostic criteria are lacking, the manufacturer will need to elucidate these, explore how the diagnostic process will work in practice, and identify any organisational implications. HTA agencies will also look to identify patient subgroups who receive the most benefit from a new technology, so exploring potential subgroups early can be of benefit to manufacturers. Furthermore, in order to qualify for NICE's Highly Specialised Technologies (HST) process, the target patient group must be 'distinct for clinical reasons'. Similarly, the Scottish Medicines Consortium (SMC) ultra-orphan process requires the condition, which is defined as a recognised distinct disease or syndrome which may be broader than the population in the license, to have a prevalence of ≤1 in 50,000 in Scotland (see Section 9 for more detail).

Therefore, careful consideration of the condition, target patient population, and diagnostic process is essential. There is often a paucity of evidence of these topics in the scientific literature, so manufacturers should endeavour to work closely with local clinical and patient experts to explore this from an early stage.

Challenge 3: Limitations in trial duration and size

The challenges that ATMP manufacturers face in generating evidence will vary depending on the condition and the value proposition. As many ATMPs are developed for severe diseases with small populations, trials may by necessity be small.

Small trial populations can compromise the reliability of statistical analyses, including:

1. Adjustments to handle high rates of cross-over from one treatment arm to another, which are often necessary for treatments with a high expected treatment benefit.
2. Analyses of the effect of covariates (patient characteristics that are predictive of outcomes), which are often necessary to inform indirect treatment comparisons for single-arm trials.

Furthermore, detailing trial duration before regulatory approval and HTA may be limited in cases where there are no effective alternative therapies and a large treatment benefit is expected, due to a desire from the authorities to accelerate patient access to the ATMP. This can further increase the uncertainty due to an absence of evidence on long-term effects of the treatment and a paucity of data upon which to base extrapolations of treatment effect, for example, overall survival (see Section 8 for a discussion on long-term survival extrapolation).

4. Considerations for clinical study design of ATMPs

There are no simple solutions to these problems that will be applicable to all ATMPs, but the following may all contribute to the value story:

- Careful consideration of the evidence preferences and perspectives of target audiences.
- Gold-standard statistical methodology to maximise use of the trial data.
- Appropriate use of real-world evidence to supplement the trial data.
- Structured elicitation of clinical judgement to address remaining evidence gaps and aid interpretation.

Deciding as early as possible how the value case will be made allows the trial design to be tweaked to minimise the impact of any limitations, for example, by including the collection of factors that are expected to be prognostic of outcomes to allow for statistical adjustments. In addition, it maximises the time available to identify evidence gaps to fill as a priority, implement appropriate research methods and subject novel evidence to peer review via journal and conference publications to help strengthen the value case before HTA submissions.

Challenge 4: Lack of head-to-head comparisons

Due to small patient populations, unclear comparators, and ethical considerations, ATMP manufacturers may be reliant on evidence from single-arm trials or observational studies. While UK and other national HTA agencies will disapprove of such designs when they believe a comparative trial was possible, there is a growing acceptance that randomised controlled trials are sometimes impractical or unethical and less robust evidence can be accepted.

Nevertheless, manufacturers will need to demonstrate they have made every effort to robustly assess comparative effectiveness where head-to-head randomised controlled trial data are lacking. During trial design, it is particularly important to anticipate the need for statistical analysis and ensure that evidence on key covariates is captured in the trials themselves. This should ideally be informed by early consideration of the covariates that have been identified in the literature, by clinicians, and via early scientific advice. This will also require a thorough review of the availability, accessibility, quality and generalisability of alternative data sources, such as patient registries and observational studies. Patient-level data are preferable where obtainable but cohort-level data from the literature may be useful where these are lacking.

To ensure comparability between the trial cohort and the cohort in the observational study it is important to 'emulate' the design of a randomised clinical trial when planning such an analysis.[7] Specifically, a clear research question should be articulated; a common baseline should be identified and wherever possible prognostic covariates should be drawn from the 'trial start' baseline. This may be more difficult to implement than initially imagined as many observational datasets often contain covariates from the point of patient diagnosis instead being repeatedly captured, hindering a robust comparison if the intervention is in a later line of treatment.

While indirect comparisons will always face scrutiny from HTA agencies, early strategic planning can help to minimise issues through inclusion of key covariates in clinical trials and identification of both a suitable comparator data source and statistical methodology. Leaving sufficient time for peer-reviewed publication is advantageous whenever possible. For further discussion on identifying the optimal approach for estimating relative effectiveness, see Section 8.

4. Considerations for clinical study design of ATMPs

Challenge 5: Difficulty measuring quality of life

UK HTA agencies require manufacturers to conduct an economic evaluation which measures health outcomes in QALYs, a compound metric of overall survival and HRQL. The EQ-5D, a quality of life instrument that can be applied to multiple conditions, is the preferred measure of HRQL in adults. However, a key challenge for ATMP manufacturers is to measure HRQL adequately. This is because small sample sizes and short trial durations (see Challenge 3) can make it impossible to demonstrate a benefit with disease-specific HRQL instruments, let alone generic measures such as EQ-5D, which will be less sensitive. Furthermore, the changes in HRQL that are important in demonstrating value for transformative therapies are commonly those that occur beyond the trial period, perhaps over many years. For flexibility in demonstrating value, manufacturers should consider using a validated disease-specific instrument alongside a generic instrument (such as EQ-5D) in clinical trials. Where disease-specific instruments are lacking, creating or validating a measure in collaboration with clinical and patient experts is an important step that is all-too-often neglected by manufacturers, and needs to be considered and addressed as early as possible to ensure it is validated appropriately to support the outcomes of the trial. If this is not possible, HRQL can be derived from vignette studies, or analogous disease areas contextualised by clinical input on their generalisability to the population of interest. A hierarchy of preferred HRQL methods for when EQ-5D is not available or is not appropriate has been proposed as part of NICE's ongoing methods review, and manufacturers should refer to this if/when available.[8]

Finally, it is worth noting that both NICE and the SMC are willing to include a treatment's impact on caregiver HRQL in economic evaluations (see the NICE and SMC Methods Guides [9, 10]). Therefore, to ensure the full value of the product is incorporated in a submission, manufacturers should consider whether an ATMP is likely to have a measurable impact on caregiver HRQL and make efforts to capture this where relevant. This may be particularly important in conditions that affect the young, or have a substantial impact on mobility or cognition.

Challenge 6: Weak link between trial outcomes and patient-relevant outcomes

Trials evaluating ATMPs are more likely than less advanced therapies to utilise surrogate outcomes (such as progression-free survival) instead of patient-relevant outcomes (such as overall survival). This is because surrogate endpoints are quicker and easier to apply, enabling shorter trials and quicker regulatory review.[6] Unfortunately, this compounds the uncertainty at HTA, as there is no guarantee that improvement in a surrogate outcome translates to a patient-relevant benefit, and any link may be dependent on covariates.

If it is known that the pivotal trial for an ATMP will focus on a surrogate outcome, ATMP manufacturers should explore the surrogacy relationship with the following hierarchy of evidence in mind:[11, 12]

- **Level 1:** Treatment effect on surrogate outcome corresponds to treatment effect on patient-relevant outcomes (for example, via a meta-analysis of randomised controlled trial data with interventions with a comparable mechanism of action).
- **Level 2:** Association between surrogate outcome and patient-relevant outcomes (for example, an observational study showing correlation of the outcomes).
- **Level 3:** Biological plausibility of relationship between surrogate outcome and patient-relevant outcome (for example, mechanistic data supporting a causal link).

Of course, for ATMPs, it will often be impossible to attain Level 1 evidence in the relevant patient population and with the relevant intervention, while Level 3 evidence is the minimum that needs to be demonstrated. In all cases, appraisal committees will want to see that an effort has been made to validate the link using a combination of statistical analysis of patient-level data from clinical trials, real world evidence, literature reviews and structured expert elicitation. Importantly, publication of findings in a peer-reviewed journal before HTA will bolster the credibility of the analysis and may be critical to its acceptance.

4. Considerations for clinical study design of ATMPs

Challenge 7: Unclear impact on resource use and service provision

ATMPs are by their very nature disruptive and can lead to substantial changes in healthcare service provision. Where ATMPs are essentially curative, there may be substantial cost offsets through prevention of the need for expensive, chronic treatments (for example, a preventive cure for Alzheimer's Disease that must be administered to healthy middle-aged adults[13]). In the UK and elsewhere, it is necessary to characterise the organisational changes required to introduce a new technology, and this will be particularly pertinent for ATMP manufacturers.

Where healthcare resource usage data are absent from clinical trials, estimates can be obtained through literature reviews focusing on the indication of interest (or analogous indications where needed) and through elicitation exercises with local experts. Patients and caregivers who have experience of receiving the new medicine can also prove a valuable source of evidence for the impact the new medicine is likely to have on these costs, which can strengthen the value proposition. Furthermore, where a medicine is likely to result in a reorganisation of service provision, manufacturers should consider the costs of funding aspects of care that need to be introduced from scratch (for example, a homecare service), as it may be worthwhile to fund this in return for reimbursement.

Proposed framework

Taking together the challenges and proposed solutions presented above, there are a few key themes that are worth highlighting:

- Many of the challenges can be mitigated through relatively minor adjustments to the design of the pivotal study (for example, collection of covariate data to support post-hoc statistical adjustments).
- Many of the solutions involve supplementary evidence generation, which take time to complete.
- Many of the solutions require the involvement of technical experts beyond the clinical development team, including statisticians, health economists, and qualitative researchers.
- Many of the solutions require collaboration with numerous stakeholders, including clinicians, patients, caregivers and HTA agencies.

Therefore, our recommendation is to initiate early strategic planning, with both regulatory and HTA processes in mind, ahead of the design of the pivotal trial. This will (i) ensure that the pivotal trial collects the most appropriate information for both regulatory and HTA audiences and (ii) allow robust evidence generation activities to be initiated to address evidence gaps that cannot be filled as part of the clinical trial.

This strategic planning process should include consideration of:

- The likely population, intervention, comparators and outcomes that will be considered at HTA.
- The aspirational value proposition for the product, with consideration of the perspectives of target audience.
- The cost of goods, as this can be particularly high for some ATMPs and may indicate how much value will need to be demonstrated.
- Key drivers of cost-effectiveness through early economic modelling (for example, survival, HRQL, cost offsets, etc.).

Where the technical expertise required is not available in-house, it is recommended that this is done in collaboration with external experts with experience of helping manufacturers with UK HTA processes. In addition, early engagement with NICE via their Strategic Advice process (see Section 9) may be worthwhile.

Early strategic planning as described above requires a small investment of time relative to the organisation of trials and therefore carries a relatively low risk. This often-overlooked step can result in a large return on investment, through optimisation of the evidence base for HTA and reimbursement discussions – thus leading to earlier access to market, approval in broader patient populations, and agreement on a price that better reflects product value. Moreover, given the large influence of NICE and SMC on other markets, planning for UK HTA at this early stage confers several synergistic benefits that are likely to support submissions in other countries.

5. Regulatory approval and beyond

Early Access - promising innovative medicine and early access to medicines schemes

Introduction

Promising innovative medicine (PIM) and early access to medicines schemes (EAMS) provide early access to medicines not yet available as licensed products. These schemes provide innovative treatment for patients with seriously debilitating or life-threatening conditions.

This is a two-step process:

- PIM designation – valid indefinitely
- EAMS scientific opinion – valid for 1 year but can be renewed

This section guides you through the application process, with downloadable templates to facilitate your submission. The advantages and disadvantages of obtaining a PIM and/or EAMS are highlighted to support your overall market access strategy.

EAMS was launched in 2014 to provide patients who have seriously debilitating or life-threatening conditions with access to medicines which do not yet have a marketing authorisation and where there is a clear unmet medical need. There is no set limit on the numbers of products entering the EAMS scheme, provided they fulfil the scheme's criteria.

Under EAMS, the MHRA will provide a scientific opinion regarding the benefits to risk ratio of the medicine, based on the data available at the point of the EAMS submission. It is usually applied to medicines which have completed Phase III trials, although under exceptional circumstances it may be applicable for products that have completed Phase II trials.

This opinion stands for 1 year and can be renewed.

The scheme is voluntary and any EAMS opinion provided by the MHRA is temporary and will be superseded by any decision through existing licensing European Medicines Agency (EMA)/MHRA procedures.

The EAMS process can provide an opportunity to generate real-world patient data – the expectation is that medicines with a positive scientific opinion could be made available to patients up to 12 to 18 months ahead of the formal marketing authorisation.

A company provides the medicine free of charge to the NHS during the EAMS period which is defined as after the award of an EAMS positive scientific opinion and up to the granting of the marketing authorisation. Those patients receiving a free of charge medicine during this EAMS period will continue to do so up to the point of a positive funding policy (for example, HTA guidance, national funding policy, local funding arrangements etc).

Companies will also need to agree on clear exit strategies with relevant bodies for the following situations:

- If no marketing authorisation is granted
- If an HTA guidance/commissioning decision is negative

It is worth noting that the implications of the UK's exit from the EU on the future position of PIM designation and EAMS is somewhat uncertain.

5. Regulatory approval and beyond

EAMS criteria

The criteria of suitability for an EAMS application are:

1. Life-threatening or seriously debilitating conditions, without adequate treatment options – high unmet need. This could include medicines intended for the treatment, prevention or diagnosis of diseases.
2. The medicinal product is likely to offer a significant advantage over methods currently used in the UK.
3. Potential adverse effects likely to be outweighed by the benefit i.e. the benefit/risk ratio is concluded as being positive.
4. The applicant is able and willing to supply the product and to manufacture it to a consistent quality standard (GMP).

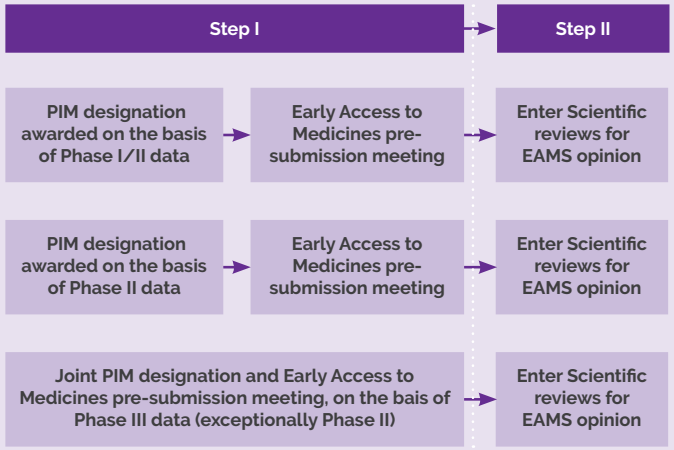
The scientific opinion will be provided after a 2-step evaluation process:

1. PIM designation
2. The early access to medicines scientific opinion

PIM designation and process

The PIM designation provides an indication that a product may be eligible for EAMS and intended for the treatment, diagnosis or prevention of a life-threatening or seriously debilitating condition with the potential to address an unmet medical need. The designation will be issued after an MHRA scientific designation meeting on the basis of non-clinical and clinical data available on the product, in a defined disease area. Often, this PIM designation is issued after the MHRA has held a scientific meeting and this designation can be provided several years before the product being licensed. If successful, the manufacturer retains control over the public release of information on the award of a PIM designation.

Figure 1. The PIM designation and process



Key: EAMS, Early Access to Medicines Scheme; PIM, Promising innovative medicine

EAMS scientific opinion

The scientific opinion primarily aims to describe the associated risks and benefits of the medicine based on data which has been collected from patients who will benefit from the medicine. This opinion supports both the patient and the prescriber in order to make a decision regarding the use of the medicine before its license is approved.

Useful links: PIM designation, how to apply, fees and next steps accessed at **https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/375327/PIM_designation_guidance.pdf**

5. Regulatory approval and beyond

Regulation in the UK after exit from the European Union

Routes to marketing authorisation

Following the UK's withdrawal from the EU, the EMA is no longer responsible for the regulation of medicines in Great Britain (England, Scotland and Wales), and this responsibility has transferred to the UK's MHRA. Marketing authorisations approved in the EU centralised procedure will automatically have effect in Northern Ireland. Northern Ireland may also be included in decentralised or mutual recognition procedures as a Concerned Member State.

The various national and international routes to obtaining a marketing authorisation are summarised in Table 1.

Useful links: Apply for a licence to market a medicine in the UK, accessed at **https://www.gov.uk/guidance/apply-for-a-licence-to-market-a-medicine-in-the-uk**

Table 1: National and international routes to marketing authorisation

Route	Jurisdictions	Duration	Notes
National routes			
National Procedure	UK, GB, or NI	150 days	This national accelerated procedure is available for high-quality applications
Innovative Licensing and Access Procedure (ILAP)	UK, GB, or NI	Unspecified	Aims to accelerate the time to market and facilitate patient access for innovative medicines, including new chemical entities, and biological medicines, new indications and repurposed medicines
Rolling review	UK, GB, or NI	Unspecified	Permits the submission of your application in module(s)
European Commission Decision Reliance Procedure	GB	67 days	For products under evaluation or approved in the EU centralised procedure, GB may rely on decisions taken by the European Commission when considering the approval of new marketing authorisations
Mutual Recognition or Decentralised Reliance Procedure	UK or GB	67 days	MHRA may have regard to marketing authorisations approved through European decentralised (DC) and mutual recognition (MR) procedures, with a view to granting a marketing authorisation in the UK or GB
Unfettered Access from Northern Ireland	GB	67 days	Applicants may seek recognition in GB of a marketing authorisation approved in NI under certain qualifying conditions
International routes			
Access Consortium	UK, Australia, Canada, Singapore and Switzerland	Unspecified	The Access Consortium consists of health regulatory agencies from Australia, Canada, Singapore, Switzerland and the UK. The Access procedures can be used to market a medicine in two or more of the countries listed. The Access consortium has developed two worksharing procedures for New Active Substances and for Generic Medicines.
Project Orbis	US, Australia, Canada, UK, Singapore and Brazil	Unspecified	Project Orbis is a programme coordinated by the US FDA involving the regulatory authorities of Australia, Canada, the UK, Singapore and Brazil to review and approve promising cancer treatments. It provides a framework for concurrent submission and review of oncology products among international partners and aims to deliver faster patient access to innovative cancer treatments with potential benefits over existing therapies, across the globe. Project Orbis submissions should also meet the qualifying criteria for the Innovation Passport within the Innovative Licensing and Access Pathway (ILAP).

Key: FDA, Food and Drugs Authority; GB, Great Britain; MHRA, Medicines and Healthcare products Regulatory Agency NI, Northern Ireland; UK, United Kingdom.

5. Regulatory approval and beyond

The Innovative Licensing and Access Procedure (ILAP)

ATMPs are likely to be eligible for the MHRA's new ILAP process, so further detail on this process is provided below.

The ILAP provides opportunities for enhanced interactions with regulatory authorities and additional stakeholder input from NICE, the SMC, NHS England and NHS Improvement, and other organisations such as the Health Research Authority (HRA) and National Institute for Health Research (NIHR).

Timing of entry into the ILAP can vary and is dependent on the stage of development of the product, the available data, the desire of the applicant to engage with UK stakeholders and to engage in innovative ways of working. Applicants are encouraged to apply early in the development of their products to maximise the benefits of the process, and products that are towards the end of the development are generally not considered suitable. As it is possible to enter the ILAP based on non-clinical data, ATMP manufacturers should consider their appetite for this process at a very early stage.

Useful links: ILAP, accessed at **https://www.gov.uk/government/publications/innovative-licensing-and-access-pathway-ilap-for-medicines/about-the-pathway**

6. Horizon scanning

The importance of horizon scanning by HTA bodies

Introduction

Horizon scanning provides information to Government and HTA bodies about products likely to require appraisal in the future. It allows the health service to prepare for cost impact and implementation of guidance well in advance of change. NICE relies on horizon scanning to set its priorities for topic selection, determining which products it will actually assess. This section briefs you on the role of UK PharmaScan and the National Institute for Health Research Innovation Observatory (NIHRIO) in this process, the steps required when making a submission for horizon scanning, and how you can make the most of the process.

Horizon scanning aims to provide advance notice to the Department of Health and Social Care (DHSC), National Institute for Health and Care Excellence (NICE), and other health service policy-making bodies and research funders of significant new and emerging technologies, up to three years before launch in the UK, that need:

- Further research or evaluation
- Consideration of clinical and cost-effectiveness
- Consideration of cost impact
- Consideration of implementation requirements
- Modification of clinical guidelines

What is UK PharmaScan?

UK PharmaScan is a database of information on new medicines, indications, and formulations in the pharmaceutical pipeline. It is the primary source of information used by all of the UK's national horizon scanning organisations and NHS England to enable early engagement in planning and preparing the NHS for the introduction of new medicines, and to support faster NHS adoption. It is populated by companies on a confidential and secure platform.

Early engagement and NHS planning have been shown to improve the speed of medicines uptake. By regularly entering comprehensive information on pipeline medicines into UK PharmaScan, product developers ensure the NHS horizon scanning organisations have the information they need.

Methodology of UK PharmaScan

Pharma Companies enter data on new medicines/indications/formulations in the pharmaceutical pipeline:

- **From 3 years before UK availability OR start of phase III (whichever is earlier**
- **Until marketed in the UK**

Information updated continously and immediately in response to regulatory changes

NHS England and UK horizon scanning organisations use the data in:

- **Pathway and system planning**
- **Development of health technology appraisal (HTA) schedules**
- **Production of briefings and resources for NHS in England, Scotland and Wales**

6. Horizon scanning

Why is UK PharmaScan important for your business?

UK PharmaScan is an essential first step in securing market access for new medicines. Early engagement and NHS planning have been shown to improve the speed of medicines uptake. Underpinned by the information available through UK PharmaScan, this planning relies on regular and comprehensive data entry by product developers.

Providing timely and relevant data enables the UK's national horizon scanning organisations to inform key stakeholders in the NHS in England, Scotland, Wales and Northern Ireland, so they can plan for the introduction of new medicines, indications and formulations. This is essential to ensure the NHS can optimise the delivery of new medicines to patients.

Who uses UK PharmaScan?

Over 240 companies are currently registered to use UK PharmaScan ranging from small biotech to global top 10 companies to enter data on their new medicines.

Which horizon scanning organisations have access to UK PharmaScan?

All of the UK's national horizon scanning organisations and NHS England use UK PharmaScan to enable early engagement in planning and preparing the NHS for the introduction of new medicines.

NHS England and NHS Improvement
https://www.england.nhs.uk/
Horizon scanning is a vital tool to understand the future healthcare environment and UKPharmaScan is a key source of data to help NHS England plan for future healthcare interventions. UK PharmaScan is therefore an essential first step for manufacturers in their market access preparations.

NIHR Innovation Observatory
http://www.io.nihr.ac.uk/
National Institute for Health Research Innovation Observatory (NIHRIO) uses UK PharmaScan to ensure that information on new and repurposed medicines, that are actively being monitored, is up-to-date and reliable. This allows us to produce timely and accurate horizon scanning intelligence to notify NICE and other national organisations to support decision-making and planning for the future.

National Institute for Health and Care Excellence
https://www.nice.org.uk/
NICE uses UK PharmaScan to track licensing information as part of the topic selection, scoping and assessment stages of the Technology Appraisal and Highly Specialised Technologies programmes. This ensures we are able to produce national guidance that enables funding and patient access to medicines within a few months of marketing authorisation.

Specialist Pharmacy Service
https://www.sps.nhs.uk/
UK PharmaScan is our go-to resource for information on UK pipeline products. It is able to provide data for NHS planning purposes that no other resource can.

Scottish Medicines Consortium
https://www.scottishmedicines.org.uk/
UK PharmaScan is a key source of information in the production of our annual horizon scanning report, Forward Look, which informs financial planning for emerging new medicines in all Scotland's Health Boards and National Specialist Services. It also highlights new medicines, indications and formulations for future health technology appraisal in Scotland.

All Wales Therapeutics and Toxicology Centre
http://awttc.org/
Information in UK PharmaScan is key in helping us support health boards and trusts across NHS Wales plan for new medicines, indications and formulations, in particular those with significant budgetary and/or service delivery implications.

6. Horizon scanning

What is UK PharmaScan used for?

The NHS needs advance information on new medicines for budget and service planning. The horizon scanning bodies across the UK deliver reports to enable better:

- National planning: informing processes and timetabling for HTA by NICE, SMC and AWMSG
- Local planning: supporting local budget. planning, formulary development and service design.
- Development of commissioning polices for new medicines.

What are the benefits for the industry?

Benefits for industry include:

- Uptake of new medicines will be enhanced because, via the horizon scanning organisations, the NHS receives consistent, timely and comprehensive information on new medicines.
- Pharmaceutical companies will save time and resource because the need to provide the same information to multiple organisations will be reduced.
- Contact between horizon scanning organisations and companies can be focused on the interpretation of product information.

Do companies need to pay to register?

No. UK PharmaScan is provided free to all pharmaceutical companies wishing to register.

What are the benefits for the horizon scanning organisations?

Horizon scanning organisations can go directly to UK PharmaScan for comprehensive and up-to-date information on new medicines. Without access to this information, each organisation would have to search for information that is in the public domain and may not be accurate or up-to-date. Where information is provided on UK PharmaScan, contact with companies can then be productively focused on the interpretation of product information rather than the provision of information.

What information does the database contain?

UK PharmaScan contains information on medicines in clinical development from up to three years before UK launch or the start of phase III clinical development (whichever is earlier).

Sections of UK PharmaScan records include:

- Technology information, including information on mode of action, route of administration, formulation, dose, British National Formulary class, likely comparators.
- Clinical trial information.
- Regulatory information, such as regulatory procedure and status, date of regulatory submission, estimated European licence date, estimated UK availability.
- Costs and budget impact information.

Depending on the stage of clinical development, it may not be possible to complete every field of the record initially. This is not an issue as data can be entered and updated as new information becomes available.

What confidentiality safeguards are in place?

Data entered in UK PharmaScan are only accessible to the manufacturer, NHS England and horizon scanning organisations. Robust web security safeguards are in place and all organisations are covered by the confidentiality clauses in their signed User Agreements.

All organisations granted access are required to sign a user agreement that sets out roles and responsibilities, including strict adherence to commercial confidentiality.

What are the implications for companies that do not register?

Participation in UK PharmaScan is voluntary. The database is the primary route for the horizon scanning organisations to access up-to-date information needed to plan for the introduction of new medicines. As such, companies choosing not to participate may find their products disadvantaged in terms of NHS planning. In addition, companies that do not register will be contacted by each of the horizon scanning organisations and will be required to provide the same information to each, resulting in duplication.

Useful links: UK PharmaScan
https://www.ukpharmascan.org.uk/

6. Horizon scanning

Horizon scanning - NIHR Innovation Observatory

The NIHRIO was initially established in 1998 as the Horizon Scanning Research and Intelligence Centre (HSRIC), an independent research team at the University of Birmingham. In April 2017 it was incorporated into the NIHR as its horizon scanning programme, and is now based at Newcastle University.

NIHRIO aims to supply timely information to key policy and decision-makers as well as research funders within the NHS in England and Wales about emerging health technologies that may have a significant impact on patients or the provision of health services in the near future. NIHRIO notify NICE about new and emerging healthcare technologies which might be suitable for NICE topic selection and subsequently technology appraisal.

NIHRIO has a remit to identify key emerging medicines, re-purposed medicines, biosimilars, ATMPs, therapeutic vaccines, medical devices and equipment, diagnostic and predictive tests and procedures, rehabilitation aids and therapy, and public health interventions. NIHRIO does not create records for prophylactic vaccines (for example, childhood vaccinations), new screening programmes, or new food products with claimed health benefits, but does identify these products and produces reports on them when required.

Identification

The NIHRIO identification process uses two principal approaches:

- Focussed routine scanning – an ongoing 'horizontal scan' designed to identify significant and urgent advances regardless of clinical speciality.
- In-depth scanning and reviews – 'vertical scans' to focus on areas with known multiple or complex developments, or inpatient groups with significant or unmet needs.

New companies or those who have not worked with NIHRIO previously can submit a form on the website 'Let us know about your technology', informing the NIHRIO of the new product. However, the information requested is only a basic starting point.

One of the sources NIHRIO uses in Horizon scanning is UK PharmaScan. NIHRIO reviewes UK PharmaScan regularly for changes, therefore it is highly recommended that companies complete a UK PharmaScan record and keep it up to date. Should a company not wish to produce a UK PharmaScan record then it is in their interests to provide the information directly to the NIHRIO.

Contact NIHRIO by emailing **info@io.nihr.ac.uk** in the first instance.

Filtration

Once technologies have been identified they are monitored and when 3 years from license, NIHRIO starts the filtration process. This initially discards minor or incremental developments and those not of relevance to NICE. A search for additional information may be required before filtration and may involve contact with relevant commercial developers and/or clinical or technological experts in the field.

The criteria for final selection are dependent on NIHRIO's agreements with each national decision-making body, but generally include filtration around time to licence or availability in the UK, the level of innovation, and potential for impact on patients and/or health services.

6. Horizon scanning

Filtration requirements for NICE

There are product timeline requirements for the NICE topic selection, as a result, the product must be:

- At least 3 years away from licensing or launch in the UK, or
- Either:
    - o In phase III clinical trials or phase II pivotal trials, or
    - o NIHRIO has an indication the medicine will be available in the UK in the next three years, or
    - o Received a priority status that might facilitate an accelerated regulatory process (Orphan Drug Designation, Breakthrough Therapy, Priority Review, Accelerated Approval, Fast Track Designation, Priority Medicines and PIM). Please see in section opposite.

To determine if the product will fit within the NICE remit, the focus is on new technology:

- New molecular entity
- New indication (patient group, inc. sub-group)
- New formulation
- New route of administration
- New mechanism of action
- New line of treatment
- New medicine combination

If a technology is considered suitable, NIHRIO produces a filtration form that is submitted to NICE for consideration. The form includes a summary of important information regarding who is developing the technology, the target patient group, the mechanism of action, treatment schedule and future plans for UK licence.

NIHRIO is informed when NICE has come to a decision on the suitability of a technology. If NICE wishes to take the product to an HTA, they will request an evidence briefing from NIHRIO.

NICE's recent Topic selection consultation

NICE are looking for views on the proposals for the Centre for Health Technology Evaluation (CHTE) topic selection programme.

Currently each guidance producing programme has a bespoke process to identify, select and route topics. Updating these processes gives NICE the opportunity to ensure good governance and oversight.

Summary of objectives

- Consolidate existing criteria to develop a single topic selection manual.
- Align decision making and stakeholder engagement processes to improve efficiency.
- Clear communication of governance arrangements to improve accountability.
- Improve the transparency of our processes.
- Help stakeholders and the public access the information they need quickly and easily.

Useful links: NICE topic selection **https://www.nice.org.uk/about/what-we-do/our-programmes/topic-selection/topic-selection-consultation**

6. Horizon scanning

Technology briefings

If a technology is selected for further investigation, information is generally provided in the form of short technology briefings. Technology briefings vary in length and detail but typically include:

- A description of the technology
- A description of the related patient group with estimated patient numbers
- The current diagnostic or treatment alternatives
- The current research evidence of clinical effectiveness
- Details of any ongoing or related research activities

In some instances they also include:

- An overview of the possible clinical, service and financial impact

Timeframe for technology briefings and alerts

The briefing is scheduled according to available licence information as follows:

- 20 months prior to licence for new technologies
- 17 months prior to licence for new indications for technologies
- As soon as possible for priority status technologies

If a briefing is required from NICE, NIHRIO will contact the company to inform them of the scheduled briefing date and to confirm the licence dates on record. The company will have an opportunity to comment on the draft briefing once written before submission to NICE in order to maintain accuracy. The evidence briefing is then submitted to NICE, who will move to the next stages of the technology appraisal processes, after which time communication is between NICE and the company.

SMC horizon scanning

Since 2005, the SMC has produced an annual horizon scanning report (Forward Look) which provides financial planners with information to support resource and service delivery planning for the managed introduction of new medicines. The horizon scanning team reviews a wide range of information (including UK PharmaScan) on new medicines in clinical development on an ongoing basis and maintains details of these within a customised database. In addition, pharmaceutical company intelligence is critical and is obtained through the request for an annual pipeline update as well as more detailed information through completion of company medicine profiles. Horizon scanning intelligence also assists SMC in workload planning in relation to new product assessments.

Useful links: SMC guidance on horizon scanning
https://www.scottishmedicines.org.uk/media/4492/smc-guidance-on-horizon-scanning-june- 2019.pdf

The horizon scanning team can be contacted here:
his.smchorizonscanning@nhs.scot

7. HTA considerations for assessing ATMPs

Introduction

As noted in Section 3, in 2015 experts from the University of York conducted a mock HTA. This concluded that the NICE appraisal methods and decision framework are applicable to RMs and cell therapies. However, an Office of Health Economics critique of this noted that while the standard processes may be applicable to ATMPs, they may not be optimal. Furthermore, the Institute for Clinical and Economic Review in the US has deemed that adaptations to its value assessment are necessary for curative, high-impact, single or short-term therapies.[13] While any deviations from usual processes should be based on robust evidence and solid rationale, it is critical that the system should have sufficient flexibility to ensure ATMPs are not periodically rejected simply because of the challenges in generating evidence at a similar standard to, for example, relatively common oncological conditions.

This section explores some of the unique characteristics of ATMPs, their implications for HTA decision making, and the arguments supporting the need for deviation from standard processes under certain circumstances.

7. HTA considerations for assessing ATMPs

Challenges with HTA decision-making for ATMPs

Challenge 1: High levels of clinical uncertainty

As outlined in Section 4, ATMP manufacturers are likely to face several evidence generation challenges, including uncertain treatment pathways, poorly defined populations, limitations in trial duration and size, and reliance on single-arm trials and surrogate endpoints.[6] Moreover, the potentially curative nature of several ATMPs means the potential benefit is substantial, and parametric extrapolations of short-term survival data are susceptible to underestimating survival for such therapies (see Section 8 for detail).[14] This is compounded by everyone's (manufacturers, regulators, patients and clinicians) desire for accelerated access, often resulting in high levels of uncertainty for ATMPs at the time of HTA.

Uncertainty can be reduced through further data collection, but there is a trade-off here, as further data collection takes time and costs money. While higher levels of uncertainty can result in loss of health benefits due to the approval of ineffective or harmful treatments, delays associated with further data collection can result in loss of health benefits from delayed access to potentially effective treatments for patients with a very high unmet need.[15] For ATMPs, the balance has historically tended towards higher levels of uncertainty at the HTA stage, because (i) they are expected to have a substantial comparative efficacy, so the health benefits forgone by delaying are substantial, and (ii) data collection is challenging, due to several factors including disease rarity, disease heterogeneity and poorly defined surrogate endpoints.

HTA agencies will expect manufacturers to take steps to minimise uncertainty (as outlined in Section 4), and further means of managing remaining uncertainty are outlined below.

In some circumstances, the high clinical uncertainty has been managed through innovative pricing mechanisms such as outcomes-based pricing. However, it should be noted that in the UK, the NHS is generally reluctant to engage in such schemes. This is in part because of the large administrative burden that the necessary data collection would place on the NHS, and in part because NHS accounting rules mean it is challenging to delay payments substantially beyond the date of treatment. Furthermore, delayed payments are unlikely to be favoured by manufacturers, who are often driven to recoup their investment in research and development as quickly as possible.

A more viable option for managing uncertainty with proven success in the UK is coverage with evidence development (CED). Indeed, a heavy emphasis is placed on CED as part of NICE's HST process and the SMC's ultra-orphan process. Furthermore, the new Innovative Medicines Fund in England, which is due to replace the Cancer Drugs Fund, will also have further evidence collection to reduce uncertainty as a prerequisite for entry (see Section 9 for more details on HST, the SMC's ultra-orphan process and the Innovative Medicines Fund). Therefore, where some form of coverage with evidence development is likely necessary, manufacturers should consider the areas of highest uncertainty from an HTA perspective and plan what supporting studies can be done both pre- and post-marketing to reassure the decision makers that future evidence will reduce these uncertainties.

7. HTA considerations for assessing ATMPs

Challenge 2: Temporal disconnect between costs and benefits

For ATMPs that involve a one-off treatment, the costs to the healthcare provider are often borne up-front, while the health benefits to patients (and perhaps caregivers) are accrued over many years. This creates unique challenges for HTA agencies, most importantly relating to affordability and discounting.

Although UK HTA agencies are not responsible for managing the budgets of the healthcare system, there is a regular two-way dialogue between them and the relevant NHS institutions. NHS England and NHS Scotland have traditionally been wary of medicines with high upfront costs because of short-term affordability concerns. In 2017, NICE introduced a budget impact 'test' in their technology assessment and HST programmes, whereby products whose annual net budget impact (in any of the first three years after launch) is expected to exceed £20 million, are subject to additional commercial discussions, and potentially a 'phased' introduction into the NHS.

One potential solution to the affordability issue that has frequently been proposed in the literature is the notion of leased payments (in other words, spreading payments over time).[6, 16] However, as outlined above, the NHS has thus far been unwilling or unable to agree to payment structures involving a substantial delay between receipt of the therapy and transfer of payment. To date, this lack of flexibility does not appear to have prevented ATMPs from being approved in the UK (many have been approved with simple percentage discounts on the list price[17]), although this may have led to delays in some cases due to extended negotiations.

The approach to discounting of future costs and health benefits also presents a challenge to decision-makers. In economic evaluation, it is important to account for the differential timing of costs and benefits in decision-making.[18] However, there is some debate as to whether standard discounting methods unfairly discriminate against treatments with high up-front costs and substantial long-term health benefits. The standard discounting approach utilised by NICE and the SMC is to apply a discount rate of 3.5% per year for both future costs and future health benefits.

This figure derives from the UK Government Treasury Green Book and attempts to incorporate 'time preference' (the preference for value now rather than later) and the 'wealth effect' (the idea that future consumption will be higher relative to current consumption and is expected to have a lower utility). However, there is some debate as to whether an additional factor should be considered in determining the discount rate for future health benefits – the potential increase in the future value of health effects.[19] Based on this, it has been estimated that health benefits should be discounted at a rate that is 1–3.5% lower than the discount rate on costs.[19] On the other hand, non-uniform discount rates have been challenged, partly on the grounds that they result in a paradox whereby perpetually delaying the introduction of the technology improves the cost-effectiveness ratio.[20]

In light of this long-standing debate, NICE allows alternative (non-reference case) discounting of both costs and health benefits at 1.5% per year as part of the HST process in defined circumstances:

- It is highly likely that, on the basis of the evidence presented, the long-term health benefits are likely to be achieved.
- The introduction of the technology does not commit the NHS to significant irrecoverable costs.

In addition to this, there seems to be an increased willingness to consider the 1.5% discount rate under the STA process, as part of NICE's ongoing methods review.[8]

ATMP manufacturers should be aware of the nuances of this ongoing debate and any key aspects of the technology which provide rationale for a discount rate of 1.5%, given that this will improve the cost effectiveness of ATMPs with high upfront costs and long-term health benefits in comparison with the reference case. Where there is some justification for a lower discount rate, including this as a scenario analysis in the submission to demonstrate its impact on cost effectiveness may be worthwhile.

7. HTA considerations for assessing ATMPs

Challenge 3: Capturing the full value of ATMPs

In the UK, HTA is primarily based on economic evaluation with health effects expressed in QALYs. QALYs combine survival and HRQL into a single composite measure and are used because they allow interventions to be compared across therapy areas. In theory this allows decisions to be made that optimise resource allocation across the entire healthcare system.

In practice, both NICE and the SMC recognise that the QALY does not capture all aspects of a product's value to society. They have therefore published explicit decision modifiers that apply under certain circumstances. However, whether these decision modifiers reflect societal preferences is questionable, and there may be some elements of value of ATMPs that are not captured within existing frameworks.

Firstly, while NICE states that HRQL should be measured using a generic measure, such as EQ-5D where possible, it has acknowledged there are two groups for whom measuring HRQL is particularly challenging: children and young people, and caregivers.[8] Both groups have a disproportionately high likelihood of being recipients of health benefits conferred by ATMPs, creating significant challenges in quantifying the full potential HRQL in these appraisals.

Secondly, there are examples of societal and patient preferences that are not adequately captured in the cost per QALY calculation or in existing decision modifiers.

These include:

- The rule of rescue – society's desire to rescue identifiable individuals at immediate risk (for example, patients with a short life expectancy at diagnosis or the initiation of treatment).[21]
- The value of hope – patients' willingness to take larger risks (for example, where there is greater uncertainty or an immediate mortality risk) in an end of life context if there is a significant chance of increased long-term survival.[22]

These preferences may be particularly pertinent to ATMPs, as they are often targeted at very severe diseases with high unmet need and limited treatment options. Although these may to some extent be covered by NICE's increased willingness-to-pay threshold for end-of-life for life-extending medicines, it is feasible that some ATMPs will confer value to society and/or patients based on these principles yet do not meet the end-of-life criteria. However, it is worth noting that NICE has indicated that the existing end-of-life criteria may be replaced with an alternative decision modifier based on disease severity in their ongoing methods consultation. It will be interesting to see whether these issues are addressed as part of this review.[8] More detail on the ongoing methods consultation can be found on the NICE website.

Thirdly, some ATMPs have the potential to replace long-term disease management with a single therapy, substantially reducing the time patients spend in hospital. This confers obvious long-term benefits in terms of increased patient quality of life and reduced burden on the healthcare system, which should be captured as part of a cost per QALY calculation. However, in addition to this, the COVID-19 pandemic is likely to have increased the preference of both patients and healthcare providers for treatments that minimise time spent in a hospital environment.

Finally, ATMPs by their very nature are innovative and transformative, often paving a path for future technologies with a related mechanism of action in different therapeutic areas. This 'scientific spillover' confers value to health systems that may not be captured within a cost per QALY calculation.[6] Despite this, innovation of itself is not valued in practice by UK HTA agencies, aside from the direct patient benefit that the product confers. While experience shows that UK decision-makers find creative means of approving innovative products even when cost effectiveness has not been clearly demonstrated (for example, via the use of decision modifiers), formally incentivising innovation (for example, as in Italy) could prevent unnecessary delay in patient access to ATMPs and encourage future innovative medicine development.

7. HTA considerations for assessing ATMPs

Challenge 4: Ethical considerations

ATMPs, particularly those involving gene editing, raise several ethical implications, many of which will be considered at the regulatory stage. For example, the legitimacy of sharing a patient's genetic data (particularly for children), the ownership of a treatment that derives from a patient's own organic tissue, and the fact that the cytokine response syndrome that can be provoked by CAR T-cell therapies is potentially fatal, all require careful consideration.[23]

Additionally, ATMPs present HTA with several ethical considerations; for example, the extent to which the voice of the patient (and the caregiver) is included in HTA deliberations. Evidence shows HTA agencies have been slow to adjust to the potential value of ATMPs.[24] Furthermore, while HTA committee members may be familiar with the nuances of more common conditions, they may be less aware of the relative significance of different aspects of rare diseases with high patient burden, which ATMPs are disproportionately designed to treat. Therefore, it is essential that the patient perspective is formally considered as part of ATMP appraisals. While NICE's HST process and the SMC's Patient and Clinician Engagement (PACE) process allow for more substantial involvement of patients in discussions, many ATMPs have been assessed via NICE's standard process, where adequate consideration of the patient experience may be lacking and should be encouraged by the manufacturer.

Conclusions

Several concerns about the applicability of standard HTA processes to ATMPs have been raised in the literature and continue to be debated. Partly in response to the launch of cell and gene therapies, NICE is currently updating its methods guide for assessing new technologies[8], with changes due to be implemented in late 2021. As with ICER, NICE's guidance considers which modification factors should be incorporated when assessing a technology's value, and how the uncertainty surrounding a technology's extrapolated treatment benefit should be characterised.

Despite the arguments supporting greater flexibility in the appraisal of ATMPs outlined above, HTA agencies will be under pressure to constrain costs in order to ensure the long-term sustainability of the healthcare system. This is because the sheer volume of ATMPs in development, combined with their high cost, is creating concerns about financial sustainability for the UK healthcare system. One study estimated that 1.1% of NHS Wales' annual budget will be spent on ATMPs in the 2020/21 financial year and this is set to rise, despite ATMPs only being allocated to 0.00063% of the population.[17] UK HTA agencies are therefore forced to find a delicate balance between rewarding innovation and budget considerations, and ATMP manufacturers would be wise to be mindful of that during engagement with these agencies.

8. Principles of health economic review

Introduction

For many years, HTA agencies in the UK have been world-leading in the use of economic evaluation as part of decision-making. This poses a unique challenge to manufacturers seeking reimbursement in the UK, and these challenges are exacerbated for ATMP manufacturers, where standard decision criteria may not be fully applicable (see Section 7).

In this section, we begin by outlining the basic requirements for economic evaluation in UK HTA, before discussing in more detail the specific issues that ATMP manufacturers will need to consider when conducting an economic evaluation.

Requirements for economic evaluation in UK HTA

For products selected for review by NICE (see Section 9 for details), the NICE methods guide 2013[9] outlines a reference case for estimating cost effectiveness, which should be followed closely when conducting an economic evaluation for submission to NICE. The NICE reference case is summarised in Table 2.

Table 2: Summary of the NICE reference case

Element of HTA	Reference case
Defining the decision problem	The scope developed by NICE as part of the scoping meeting (see Section 4 of this booklet on how this can be predicted)
Comparator(s)	As listed in the scope developed by NICE
Perspective on outcomes	All direct health effects, whether for patients or, when relevant, carers
Perspective on costs	NHS and PSS
Type of economic evaluation	Cost–utility analysis with full incremental analysis
Time horizon	Long enough to reflect all important differences in costs or outcomes between the technologies being compared
Synthesis of evidence on health effects	Based on systematic reviewww
Measuring and valuing health effects	Health effects should be expressed in QALYs. The EQ-5D is the preferred measure of HRQL in adults. Note there are two variations of EQ-5D: EQ- 5D-3L and -5L, which have 3 and 5 levels of severity, respectively. NICE prefers the EQ-5D-3L and where EQ-5D has not been collected, a mapping exercise should be conducted to estimate EQ-5D data if possible
Source of data for measurement of HRQL	Reported directly by patients and/or carers
Source of preference data for valuation of changes in HRQL	Representative sample of the UK population
Equity considerations	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit
Evidence on resource use and costs	Costs should relate to NHS and PSS resources and should be valued using the prices relevant to the NHS and PSS
Discounting	The same annual rate for both costs and health effects (currently 3.5%, although 1.5% may be used under certain circumstances as part of the HST process)

Key: EQ-5D, EuroQoL 5 Dimension questionnaire; HRQL, health-related quality of life; HST, Highly Specialised Technologies; NHS, National Health Service; NICE, National Institute for Health and Care Excellence; PSS, personal social services; QALY, quality-adjusted life year.

8. Principles of health economic review

Advice on predicting the decision problem, measuring HRQL and costs is provided above in Section 4. Where a manufacturer believes there are reasons for applying non-reference-case methods, these should be clearly specified and justified to NICE as early as possible (for example, during the scoping phase and/or decision problem meeting).

Although the SMC's Guide for Manufacturers[10] is less prescriptive than NICE's methods guide, an equivalent approach is generally advisable for the SMC. One of the key differences is that while NICE defines an explicit willingness-to-pay threshold of £20–30,000 per QALY gained (exceptions to this are discussed in Section 9), the SMC does not specifically define a willingness-to-pay threshold.

Experience shows that £20k – £30k per QALY gained is a reasonable approximation of the SMC's willingness-to-pay, although the SMC notes several decision modifiers allowing a higher cost per QALY to be accepted, many of which may be relevant for ATMPs:

- Evidence of a substantial improvement in life expectancy (with sufficient quality of life to make the extra survival desirable). Substantial improvement in life expectancy would normally be a median gain of 3 months but the SMC assesses the particular clinical context in reaching its decision.
- Evidence of a substantial improvement in quality of life (with or without survival benefit).
- Evidence that a subgroup of patients may derive specific or extra benefit and that the medicine in question can, in practice, be targeted at this subgroup.
- Absence of other therapeutic options of proven benefit for the disease in question and provided by the NHS.
- Possible bridging to another definitive therapy (for example, bone marrow transplantation or curative surgery) in a defined proportion of patients.
- Emergence of a licensed medicine as an alternative to an unlicensed product that is established in clinical practice in NHS Scotland as the only therapeutic option for a specific indication.

Economic evaluation of ATMPs

In UK assessments of ATMPs to date, two topics have been of greatest importance when assessing value: drawing reliable estimates of relative treatment benefit with non-randomised data ('unanchored' indirect treatment comparisons), and robustly estimating long-term outcomes from short-term trial data (extrapolations). Means of mitigating these challenges for ATMPs are discussed below.

Estimating relative treatment effect for single-arm trials

As discussed in Section 4, ATMP manufacturers are often forced to rely on single-arm trial data. Regardless of the nature of the comparator(s), NICE and the SMC require an estimation of the relative treatment effect of the technology, and several statistical techniques can be used to provide such estimates. For example, one of the more robust approaches for comparator analysis where only population-level data are available is to effectively simulate a comparison with the existing mix of treatments using real world evidence. An alternative, less robust, approach is to calculate relative hazard ratios using a statistical technique such as a matching-adjusted indirect comparison (MAIC).

Interestingly, despite the existence of established analytical methods that aim to adjust for imbalances in patient characteristics across treatment arms, NICE and the SMC have tended to prefer minimal or no use of statistical adjustments to inform relative effectiveness comparisons in previous appraisals of ATMPs. Simplicity in the analytical approach is therefore recommended. Manufacturers of ATMPs should focus on estimating comparator outcomes that plausibly generalise to patients in UK clinical practice, rather than using the most sophisticated statistical techniques in an attempt to minimise bias in estimating the relative treatment effect. It will be important for manufacturers to keep abreast of any changes introduced on this topic via the ongoing NICE methods review and new publications from NICE's Decision Support Unit.

8. Principles of health economic review

Estimating lifetime health outcomes

For the reasons outlined in Section 4, clinical trials for ATMPs are often short in duration. The resulting uncertainty, compounded by the advanced mechanism of action of ATMPs, often necessitates a creative approach to estimating long-term health outcomes, which is often a critical driver of cost effectiveness in UK HTA submissions.

For ATMPs where the treatment aim is to 'cure', NICE has previously been open to extrapolation approaches that enable a proportion of patients to have estimated survival close to the equivalent age-matched general population. This can be formally incorporated into economic evaluations using non-standard methodologies, such as 'mixture-cure' models, where a proportion of patients receiving a treatment are deemed to be cured (statistically cured in the sense that they have a survival prognosis equivalent to a similarly aged member of the general population). However, there are a few pitfalls here that should be avoided.

Firstly, even where evidence is available that demonstrates the technology returns patients to near-normal survival, this being framed explicitly as a 'cure,' is generally poorly received by UK agencies given that this is usually reliant on relatively short-term data. Therefore, it may be preferable to use terminology such as 'long-term survivors' or 'responders' rather than 'cured'. Secondly, any argument relating to long-term survivors needs to be anchored in the specific nature of the indication and treatment lines. For example, if the technology is being assessed for a later treatment line for an advanced oncological condition, it may be seen as implausible that a large proportion of patients will return to a similar mortality risk to that of the age-matched general population. Therefore, the feasibility of the survival estimates produced in the economic model should be justified and validated with clinical experts. Relatedly, when selecting their base case estimate for the 'cure fraction' (or similar), the manufacturer should select one that aligns with clinically related indicators such as the proportion in durable complete/deep response.

Conclusions

For ATMP manufacturers, economic evaluation for UK HTA requires a combination of innovation and simplicity. Ultimately, the approach should be informed by precedent in previous appraisals with similarities to the medicine's setting (for example, mechanism of action, indication, positioning in treatment pathway), and the key areas of value that the product offers over existing treatments, which can be identified using the early strategic planning framework outlined in Section 4. Where it is anticipated that the reference case will not adequately capture these key areas of value, deviations may be justifiable based on the arguments outlined in Section 7.

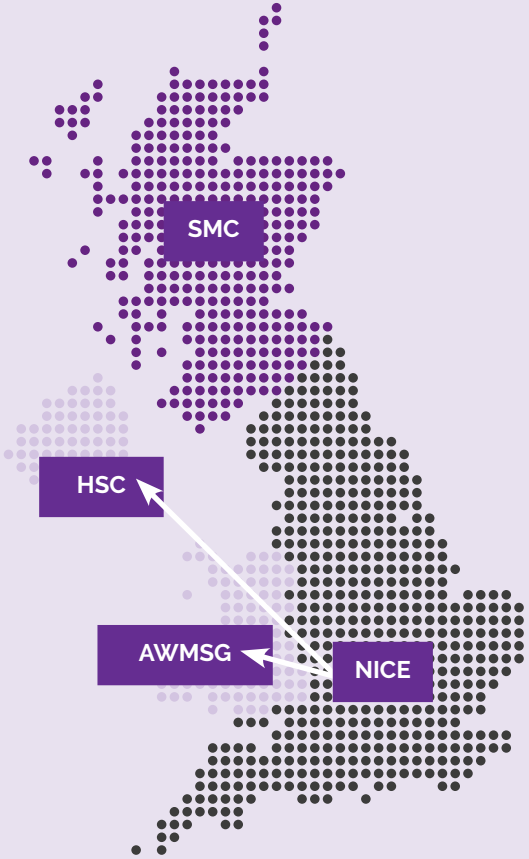
9. HTA submission considerations

Introduction to UK HTA agencies

Key agencies

In the UK, HTA processes differ across England, Scotland, Wales and Northern Ireland, as shown in Figure 2.

Figure 2. HTA agencies across the UK



Key: AWMSG, All Wales Medicine Strategy Group; HSC, The Health and Social Care Board; NICE, National Institute for Health and Care Excellence; SMC, Scottish Medicines Consortium; arrows indicate explicit influence of recommendations under certain circumstances

NICE is an executive non-departmental public body working with the English NHS, but its services are also used in varying ways in Wales and Northern Ireland. England and Wales are legally obliged to provide any technology recommended by NICE's technology appraisal. The SMC conducts its own appraisal process for assessing medicine access and reimbursement for NHS Scotland. The All Wales Medicine Strategy Group (AWMSG) appraises selected pharmaceuticals for which NICE is not intending to publish final technology appraisal advice within 12 months of the date of marketing authorisation. If technology appraisal guidance is issued by NICE in the same medicine and indication as that appraised by the AWMSG, the AWMSG advice is superseded by NICE guidance. The Health and Social Care (HSC) Board in Northern Ireland is responsible for checking legal, policy and financial consequences related to implementation of NICE recommendations (or SMC if no NICE appraisal is available) in Northern Ireland, and it makes amendments as needed.

Given the expectation that NICE and the SMC will review the vast majority of ATMPs, and therefore that NICE is likely to influence reimbursement decisions for ATMPs in England, Wales and Northern Ireland while reimbursement of ATMPs in Scotland will be primarily driven by the SMC, the rest of this booklet focuses exclusively on NICE and the SMC.

9. HTA submission considerations

NICE and SMC processes: similarities and differences

Appraisals of health technologies at NICE and the SMC follow the same overarching principles, focusing primarily on clinical effectiveness and cost effectiveness as key decision drivers. However, there are several important differences in their processes. Firstly, the timetable for submission to NICE is imposed on the manufacturer, while manufacturers have more control over the timings of SMC submissions. NICE initiates appraisals via an invitation to participate following topic selection and prioritisation, which are themselves based on horizon scanning (see Section 6). On the other hand, the SMC is less selective than NICE and deadlines for submission are not dictated to the manufacturer. A company may make a submission to the SMC for a product once it has received a positive opinion from the EMA's Committee for Medicinal Products for Human Use (CHMP) or approval from the MHRA, though the SMC can issue a 'not recommended' decision by way of a non- submission if over time a submission is not forthcoming for a product. Secondly, while there are multiple opportunities for formal engagement with NICE before and after submission (discussed below), this is not the case for the SMC as a result of it being a relatively small organisation. Finally, NICE appraisals occur via a series of Appraisal Committee meetings, between which the manufacturer can submit additional analyses or propose alternative pricing schemes. At the SMC, there is significantly less time available for discussion and decisions are made within one meeting, though there is an opportunity for manufacturers to submit additional analyses between the New Drugs Committee (NDC) meeting and SMC decision. However, while resubmission to NICE is not common and not recommended, manufacturers can submit to the SMC multiple times.

Coordination of HTA activities across the UK

Given the interplay between HTA agencies in the UK, it is important for a manufacturer to think carefully about the relative timing of submission to NICE and the SMC. It is usually preferable to submit to NICE before the SMC. This is because the population to which NICE decisions apply is significantly larger. In addition, the earliest possible submission has historically been earlier for NICE than the SMC, because in most cases the first Appraisal Committee meeting is timed to roughly coincide with CHMP opinion and the final appraisals determination with marketing authorisation, while a manufacturer is required to have a positive CHMP opinion in order to submit to the SMC. However, there may be some instances where it would be better to submit to SMC first. For example, if clinical support in Scotland is particularly strong and a positive result is expected there, it may be worthwhile to submit there first. This would allow rapid market access across Scotland in advance of the NICE submission.

Regardless of the relative timing of the submissions, there are efficiencies to be gained in preparing for submissions to NICE and the SMC with careful planning. For example, when conducting UK advisory boards, it is often useful to ensure the presence of at least one Scottish clinician to confirm generalisability of findings to Scotland. This can also allow for confirmation of the likely comparator(s), as these may differ across the two jurisdictions. While a similar submission strategy and value story may be applicable to both agencies, it is important to note that the SMC will not look favourably on material simply copied from a NICE submission, without consideration of the applicability to Scottish clinical practice.

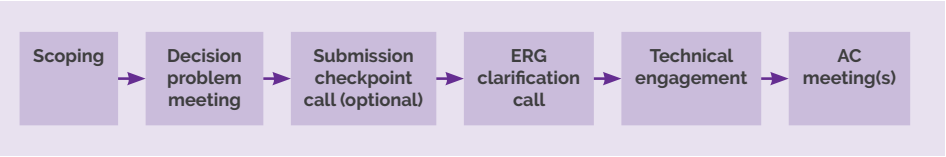
9. HTA submission considerations

NICE and NHS England

NICE pathways and processes

The various processes through which NICE assesses new health technologies are summarised in Table 3. Regardless of the specific technology appraisal programme, NICE appraisals follow the process outlined in Figure 3.

Figure 3: The NICE appraisal process



Key: AC, Appraisal Committee; ERG, Evidence Review Group.

Once a topic has been prioritised for appraisal, the appraisal topic is considered in the scoping process. Scoping allows for consultation of interested parties on the questions which the appraisal will address, with the objective of steering and focusing the appraisal. NICE develops a draft scope document which is sent out for comment. The draft sets out the population, comparators, potential subgroups, and health outcome measure. If discussion is required, a scoping meeting will be organised, and manufacturer representatives will be invited to attend. Following receipt of comments (and scoping meeting discussion, if applicable) NICE will update the scope, in anticipation of receiving a formal referral to appraise the technology from the Secretary of State for Health and Social Care. After formal referral, NICE plans the topic into the work programme, and normally publishes the detailed timelines on its website within six weeks.

Before the start of the appraisal, the company has the opportunity to discuss the decision problem that follows from the draft scope with the NICE team and the Evidence Review Group (ERG, an independent academic centre commissioned by NICE to review and critique the company's evidence submission). The discussion enables NICE and the ERG to discuss challenges, the evidence base, the economic modelling approach, any deviations from the reference case, and previous NICE appraisals in that area. Following the decision problem meeting, formal invitation is sent to consultees and commentators, which may include other manufacturers, professional associations, patient associations and others. The deadline for the evidence submission is 60 days from invitation. During the development of evidence submission, the manufacturers have the opportunity to discuss key issues with NICE and, if needed, the ERG. Details of the documents that must be completed as part of a NICE submission can be found on the NICE website.

Following submission, the evidence package is sent to the ERG for critical evaluation and during this review process the ERG will develop several clarification questions for the manufacturer to respond to. A call will be arranged to provide the manufacturer and the ERG with an opportunity to discuss these clarification questions. Following receipt of responses to the clarification questions, the ERG will produce its report. This report focuses on the key issues within the appraisal, which the committee considers alongside the manufacturer's submission. The technical engagement process will then begin, whereby the key issues will be discussed in an attempt to resolve them before the first Appraisal Committee meeting. This is a formal step which allows the manufacturer to provide additional data to reduce uncertainty, to discuss price with NICE before the first Appraisal Committee meeting, and to seek clinical expert opinion on remaining issues. Unresolved issues are then discussed by the committee in Appraisal Committee meetings, until a final appraisal determination can be made.

9. HTA submission considerations

Table 3: NICE technology appraisal processes

Programme	When is it used?	Basis of value proposition	Factors considered in decision making
Single technology appraisal (STA)	• New pharmaceutical products • License extensions for existing products • Reviews of published appraisals	• ICER less than £20k–£30k (either more benefits at higher cost, or fewer benefits at lower cost) • ICER less than £50k for end-of-life life-extending treatments	• Clinical effectiveness • Cost effectiveness • Value of technology • Budget impact
Multiple technology appraisal (MTA)	• If a new topic for an appraisal is particularly complex and not suited for the single technology appraisal process • Reviews of published appraisals	• ICER less than £20k–£30k (either more benefits at higher cost, or fewer benefits at lower cost) • ICER less than £50k for end-of-life life-extending treatments	• Clinical effectiveness • Cost effectiveness • Value of technology • Budget impact
Fast track appraisal (FTA)	• Company's base case ICER is less than £10k, likely that most plausible ICER is less than £20k, and highly unlikely that most plausible ICER is greater than £30k • Similar or greater health benefits at similar or lower cost	• Cost saving and clinically equivalent or superior • ICER less than £10k (more benefit at slightly higher costs)	• Clinical effectiveness • Cost minimisation or cost • effectiveness • Value of technology • Budget impact
Highly specialised technology (HST)	• Medicines for very rare conditions	• ICER less than £100k–£300k/QALY depending on QALY gain (higher ICERs accepted at higher levels of QALY gain, i.e 10-30 QALYs)	• Clinical effectiveness • Cost minimisation or cost • effectiveness • Value of technology • Budget impact

Key: ICER, incremental cost-effectiveness ratio; NICE, National Institute for Health and Care Excellence.

Throughout this process, experience shows that taking a collaborative and communicative approach often results in better outcomes. Manufacturers should therefore focus on working with NICE and other stakeholders to resolve uncertainties and attain the best value offer possible. This involves working with clinical experts to ensure that assumptions are credible and will stand up to the scrutiny of the ERG and NICE committee.

9. HTA submission considerations

NICE pathways for ATMPs

Given the high cost of developing ATMPs, manufacturers are unlikely to be able to price them such that they qualify for the fast track appraisal process (unless, for example, if the comparator is another ATMP or is associated with particularly high costs for other reasons). Multiple technology appraisals are also unlikely, given that ATMPs generally target diseases with few comparators. Therefore, the most likely appraisal process is the single technology appraisal (STA), although some ATMPs may qualify for the HST process, which is described in more detail below.

The Highly Specialised Technology process

HST may offer a more suitable assessment route for many ATMPs given the evidence generation challenges that manufacturers face (see Section 4). **The HST process differs from a standard STA in the following ways:**

1. The willingness-to-pay threshold is £100,000–300,000 per QALY gained

If cost/QALY is believed to be below £100k per QALY gained, and the Committee is comfortable with the level of uncertainty, the product will be approved. Above £100k per QALY, judgements consider the magnitude of benefit as revealed through the number of additional (undiscounted) QALYs expected to be gained per patient over a lifetime. Products offering 10 or fewer incremental QALYs are assessed using the £100k per QALY gained threshold, but for those offering 30 or more QALYs a weighting of 3 is applied to those QALYs such that the effective willingness-to-pay threshold is £300k per QALY gained. Where the incremental QALY gain lies between £10k and £30k, a QALY weighting of between 1 and 3 will apply on a sliding scale.

2. The Committee is encouraged to take a broader perspective on benefits and costs

Factors considered in decision making include the nature of the condition, the impact of the technology, the cost to the NHS and PSS, the value for money, indirect and non-health benefits and delivery of specialised services.

3. Patients and specialist clinicians attend the meeting and are regularly brought into the discussion by the Chair

Where data are lacking, patient and clinical experts will be asked for their opinion. Patients and clinicians are likely to be invited to make presentations and participate in discussion but are excluded from the confidential part of the meeting and cannot vote.

4. Unavoidably high levels of uncertainty are relatively well-tolerated

It is accepted that highly specialised technologies will generally be associated with higher levels of uncertainty. Nevertheless, the case for cost effectiveness is frequently lost because the clinical benefits against a relevant comparator are seen to be so uncertain as to make committee sentiment highly negative. In these circumstances a committee may choose to report its 'most plausible ICER' as being one which lies outside the threshold figure, while the real driver of the decision was doubt as to whether benefits claimed would be delivered.

5. Recommendations on the use of HSTs regularly include a managed access arrangement

The impact of uncertainty on committee sentiment can be minimised via a carefully considered proposal for managed access arrangements. These may involve further evidence collection to address significant remaining uncertainty in the evidence base; starting, stopping and continuation criteria; funding arrangements; and risk-sharing agreements. An example of the latter is the approval of funding for a technology to treat up to a maximum number of patients per year, with any patients prescribed the product over this threshold to be financed by the manufacturer.

9. HTA submission considerations

The criteria for HST are as follows:

- 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 (no defined threshold level; this is decided at NICE's discretion)
- The target patient group is distinct for clinical reasons
- The condition is chronic and severely disabling
- The technology is expected to be used exclusively in the context of a highly specialised service
- The technology is likely to have a very high acquisition cost
- The technology has the potential for lifelong use
- The need for national commissioning of the technology is significant

However, it is worth noting that the capacity of the HST Committee is highly limited (3–4 appraisals per year). As a result, many products that seem to meet these criteria are not prioritised and instead are assessed via the standard STA route. Patient groups, key opinion leaders and elected politicians carry some influence in the NICE prioritisation process. Therefore, if an HST appraisal is particularly desirable, engaging early with these stakeholders is highly recommended.

Access mechanisms within the Single Technology Appraisal process

In cases where ATMPs are appraised via the STA route, the standard cost effectiveness thresholds of £20k–£30k per QALY imposed by NICE may be unattainable to manufacturers given the need to recuperate research and development costs and the high cost of manufacturing the product. However, mechanisms exist within the STA process that may represent a route to reimbursement in these more challenging cases.

Firstly, products indicated for small patient populations that are deemed to be life-extending (normally by ≥3 months) for patients with a short life expectancy (normally <24 months), are currently assessed as End of Life (EoL) technologies against a cost effectiveness ratio threshold of £50k per QALY gained. However, NICE has indicated as part of its ongoing methods consultation that this is likely to be replaced by a new decision modifier based on disease severity.[8] This is likely to be relevant for ATMPs, so manufacturers should check the NICE website for any updates to the guidance.

Secondly, for oncology products, NICE has the option to approve a product for reimbursement via the Cancer Drugs Fund (CDF). To qualify for the CDF, the product must be plausibly cost effective at the submitted price, and uncertainty must be clinical in nature. Approval via the CDF allows for temporary coverage with evidence development, usually with an agreement to collect data via the systemic anti-cancer therapy (SACT) database. In 2020, the UK government committed to expanding the CDF to an Innovative Medicines Fund. This involves an increase in the ring-fenced budget to £500 million, and expansion to 'innovative' medicines across a range of conditions. However, the details of how innovative medicines will be defined, and the conditions associated with approval via the Innovative Medicines Fund are yet to be outlined.

9. HTA submission considerations

Opportunities for engagement with NICE and NHS England

There are multiple opportunities to engage with NICE and NHS England, both before and after submission. For ATMP manufacturers, the recommendation is to engage early and engage often, as this will minimise the risk of unexpected issues arising throughout the HTA process. The key opportunities for engagement are outlined below.

NICE Scientific Advice

NICE Scientific Advice is a fee-based consultancy service to pharmaceutical manufacturers, which aims to help with the development of evidence that demonstrates product value. This is best used at the time of clinical trial design and must be completed at least before the invitation to submit. The cost of Scientific Advice varies between £30k and £70k, depending on the complexity of the briefing and the number of experts and consultees required. A confirmed quote is agreed with the manufacturer following delivery of a briefing book to NICE. However, there is an opportunity for the manufacturer to amend the briefing book if they are not happy with the quote provided.

Advice given is non-binding and confidential and is not shared with Committees or ERGs. The manufacturer has no obligation to take the advice, but equally there is no guarantee the committee will not criticise the approach if the advice is taken.

NICE Office for Market Access

The NICE Office for Market Access (OMA) is a complimentary service to scientific advice and was set up in response to company feedback that more joined-up dialogue between stakeholders is needed. A company can engage with the OMA at any time, but not during an open appraisal (an appraisal can be on hold). While scientific advice aims to provide guidance on evidence development, OMA is generally used to seek guidance on the appraisal process. The fee for engagement with OMA is based on the company request and the number of stakeholders and experts required. On average, a 2-hour OMA meeting costs £2.5k–£8k. A half day meeting can cost up to £20k. The documents requested from the company before an OMA meeting are less detailed than the scientific advice briefing book. This should include an outline of 3–4 topics the company is requesting advice on. The company is also asked to do a 5–10 minute presentation at the start of the OMA meeting. As with scientific advice, this is a non-binding, signposting process that aims to help the manufacturer explore their options.

NICE Commercial Liaison Unit

NICE established its Commercial Liaison Unit to work with manufacturers who are considering a patient access scheme (PAS) for their technology. The unit assesses the manufacturer's proposal to check that it is compatible and implementable within the NHS. There are two categories of PAS: simple (a percentage discount on the list price) or complex (any other commercial arrangement). If a manufacturer is intending to submit a PAS, the proposal should be sent to the Commercial Liaison Unit before submission to ensure this is processed before the first Appraisal Committee meeting. The exact details of the PAS can be modified once the paperwork is in place. However, manufacturers should aim to engage with the Commercial Liaison Unit as early as possible, particularly if they intend to submit a complex PAS, as these take significantly longer to arrange.

9. HTA submission considerations

NHS England Commercial and Clinical Surgeries

Beyond the opportunities to engage with NICE outlined above, some manufacturers may benefit from requesting a Clinical or Commercial Surgery with NHS England. These can occur either before or during an appraisal and tend to occur later than NICE's Scientific Advice and OMA offerings, with the purpose of facilitating further targeted discussion on commercial and clinical issues.

Clinical Surgeries provide the opportunity for manufacturers to interface with the Specialised Commissioning team, while Commercial Surgeries may be valuable for manufacturers who are considering a non-confidential complex PAS or a Confidential Commercial Agreement. Confidential Commercial Agreements may be offered under two circumstances: (i) if the manufacturer is willing to provide an enhanced value offer (for example, a lower price) in return for the commercial flexibility, or (ii) where there are unusual or unique circumstances that mean launching a product is considered particularly challenging or commercially unviable. More detail on these processes is available in NHS England's Commercial Framework for Medicines (see Useful links on page 44).

SMC

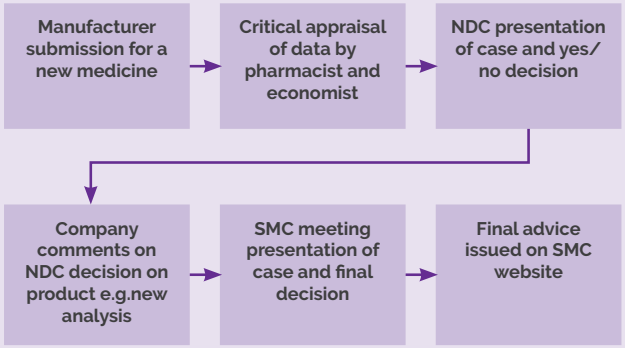
SMC pathways and processes

Submissions are made on the first Monday of the month. When a manufacturer makes a submission to the SMC, a pharmacist, health economist and a New Drugs Committee (NDC) member (known as the Lead Assessor) are allocated to review a company's submission for each full submission or resubmission being assessed. Details of the documents that must be completed as part of an SMC submission can be found on the SMC website. The SMC economist will request additional analysis from the company and validate assumptions with SMC clinical experts throughout the process. From experience, questions from the economist come in several batches throughout the appraisal, often with very tight deadlines. The NDC meets to discuss the appraisal with a purely technical remit to review the clinical and economic evidence. This committee makes the first assessment of each submission and passes its recommendation to the SMC. The decision of the NDC is shared with the company and at that juncture they have the opportunity to respond to any issues or uncertainties outlined in the draft advice; for example, by providing further supporting evidence or analysis. The company also has the opportunity to introduce a new or revised patient access scheme discount at this point to help with the cost-effectiveness of the case that will be considered by SMC.

The SMC will then hold a short public meeting and will make a judgement on the technology, potentially factoring in broader considerations than the evidence-based approach of the NDC. Manufacturers can attend these meetings but have significantly less input than at NICE Appraisal Committee meetings.

The usual assessment timeline is 18 weeks from the scheduling of a submission to publication of advice. However, a longer timeline (for example, 22–26 weeks) is required for submissions requiring PACE or a complex PAS and there are often delays to the SMC accepting a submission. The standard process for SMC appraisals is shown in figure 4.

Figure 4: The SMC appraisal process



Key: NDC, New Drugs Committee; SMC, Scottish Medicines Consortium

9. HTA submission considerations

SMC pathways for ATMPs

Ultra-orphan process

In a similar vein to NICE's HST process, the SMC offers a separate ultra-orphan process, aimed at alleviating some of the challenges associated with assessing an ultra-orphan product via the standard framework. This process allows the SMC to consider a broader decision-making framework, including the nature of the condition, the impact of the medicine, and impacts beyond direct health benefits and costs to the NHS.

The criteria for the SMC's ultra-orphan process are as follows:

- The target patient group for the technology in its licensed indication is so small that:
  - The condition has a prevalence of 1 in 50,000 or less (or around 100 people) in Scotland.
  - The medicine has an EMA orphan designation for the condition and this is maintained at the time of marketing authorisation.
  - The condition is chronic and severely disabling.
  - The condition requires highly specialised management.

A medicine must be validated as meeting the SMC ultra-orphan criteria before the initial submission, so manufacturers are encouraged to apply for the ultra-orphan process via completion of a proforma before receiving CHMP opinion. Although the broader decision-making framework may be preferable to ATMP manufacturers, it is important to note that the provision of a patient access scheme and further data collection led by the company are pre-requisites for approval via the ultra- orphan process, which may not be aligned to company strategy.

Interestingly, while in NICE's HST process the patient population size threshold is not explicitly defined, yet the increased ICER levels are, the SMC's ultra-orphan process defines explicitly the patient population size threshold, but not the impact on the ICER level that the SMC deems acceptable.

PACE

If a technology receives a preliminary 'not recommended' by the New Drugs Committee, manufacturers can request a PACE meeting. This allows for greater incorporation of the patient and clinician voice via structured discussion, focusing on areas of added value that may not be captured in a conventional assessment, such as impact on the ability to work, mental health, independence and dignity of both patients and caregivers. This is likely to be worth pursuing for most ATMPs, as it can give more substance to the decision through the presence of impartial patient groups. However, it is worth noting this may be becoming less influential due to its popularity and is no replacement for high quality empirical evidence in the original submission.

Opportunities for engagement with the SMC

Compared with NICE, there is less opportunity for direct and formal engagement with SMC stakeholders during the pre-submission stage. The SMC does not routinely meet with companies before submission, but any queries may be submitted to the SMC secretariat in writing. However, for ATMPs and a few other specific circumstances (e.g. products in the EAMS and validated ultra- orphan medicines), the SMC provides the opportunity for pharmaceutical companies to meet with SMC staff prior to submission for a newly licensed medicine. Beyond this, manufacturers should inform the SMC of their intention to submit and of any expected delays.

9. HTA submission considerations

Useful links

NICE and NHS England

- NICE Guide to the processes of technology appraisal **(https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE- technology-appraisals/technology-appraisal-processes-guide-apr-2018.pdf)**
- NICE Guide to the methods of technology appraisal **(https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology- appraisal-2013-pdf-2007975843781)**
- NICE Interim Process and Methods of the Highly Specialised Technologies Programme **(https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-highly- specialised-technologies-guidance/HST-interim-methods-process-guide-may-17.pdf)**
- NICE consultation: Reviewing our methods for health technology evaluation **(https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/chte- methods-consultation)**
- NICE Scientific Advice **(https://www.nice.org.uk/about/what-we-do/life-sciences/scientific- advice)**
- NICE Office for Market Access **(https://www.nice.org.uk/about/what-we-do/life- sciences/office-for-market-access)**
- NICE Commercial Liaison Unit **(https://www.nice.org.uk/about/what-we-do/patient-access- schemes-liaison-unit)**
- NHS England Commercial Framework for Medicines **(https://www.engage.england.nhs.uk/consultation/nhs-commercial-framework-for- medicines/)**

SMC

- Guidance on making a submission **(https://www.scottishmedicines.org.uk/making-a- submission/)**
- Guidance supplement for ultra-orphan medicines **(https://www.scottishmedicines.org.uk/how-we-decide/ultra-orphan-medicines-for-extremely-rare-conditions/)**
- Guidance supplement for submissions of medicines with EMA conditional marketing authorisation **(https://www.scottishmedicines.org.uk/how-we-decide/interim-acceptance- decision-option/)**
- Guidance on comparator medicines with a PAS **(https://www.scottishmedicines.org.uk/making-a-submission/companies/patient-access-schemes/comparator-medicines-with-a-pas/)**

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nuth.NAATTC@nhs.net @naattc

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