CELL & GENE THERAPY INSIGHTS

EXPERT INSIGHT

The route to patient access: challenges of evaluating and funding new cell and gene therapies

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Almost every patient or parent, or carer of a patient with a long-term, life-threatening or seriously debilitating condition dreams of the day when medical science can provide a 'cure' for that condition. But what is the impact on patients and the healthcare system when it looks increasingly likely that the dream may be realized but governments or other payers do not have the resources to pay for it? How should health technology assessment (HTA) organizations, such as NICE, and payers respond?

The REGenableMED Policy Briefing 2016 effectively articulates some of the issues that affect reimbursement decisions for cell and gene therapies, and highlights the difficulties inherent in accessing a market where the normal rules are perceived to be 'not applicable'.

Identifying responsibility for funding does not guarantee the availability of additional money for what are frequently innovative, potentially curative, but budget-busting, new treatments, often with high upfront costs. Additionally, at the point of launch, the evidence base for the treatment may be limited, resulting in high uncertainty with regard to long-term patient health outcomes. If there is no new money in the system, what is the potential impact on other healthcare interventions that would be displaced in order to pay for it? The need for the appropriate assessment of cost–effectiveness methods for these therapies has never been greater.

In England, it is likely that funding of most cell and gene therapies will initially fall within the remit of NHS England's Specialised Services, although local clinical commissioning groups (CCGs) may also commission some therapies and play a role in the development of service contracts. Specialized services are those provided in relatively few, usually specialist, hospitals where the number of patients with a condition is fairly small and it is easier and more cost-effective to recruit and train healthcare professionals in specialist techniques and in the use of specialist equipment.

NICE does not directly commission services, drugs, devices or other medical technologies but sets national commissioning policy through its guidance to the NHS. It is anticipated that many of these cell and gene therapies in England will be evaluated through the HTA processes of the NICE Technology Appraisals program. Some products may meet the criteria for evaluation through the Highly Specialised Technologies program. Any technology receiving a positive recommendation through these two routes comes with a funding

mandate that directs commissioners to make funds available for the technology within 90 days of the guidance being published.

The NICE Technology Appraisal framework is based on estimating patient outcome benefits in quality-adjusted life years (QALY), a metric that combines the impact of a health intervention on both the length and quality of life. 1 QALY is equivalent to 1 year of life in full health. Where a product has major impact on length and/or quality of life compared to current NHS care, the QALY gains may be sufficient to justify a high treatment cost. In estimating QALY gains, however, there will often be a need to extrapolate health benefits from short trials to much longer term outcomes, which is a major issue for treatments considered curative or at least providing benefits to patients over a prolonged period of time.

NICE co-chaired, with NHS England, the Evaluation and Commissioning subgroup of the Regenerative Medicines Expert Group (RMEG) established by the Department of Health. In response to a recommendation from RMEG, NICE, in collaboration with the University of York, undertook the study referred to in the REGenableMED Policy Briefing, to explore whether its processes, methods and decision frameworks are fit for purpose to evaluate regenerative medicines and cell therapies. It has been suggested that NICE's current methodology has limitations in its application to regenerative medicines and cell therapies. They may be particularly difficult to evaluate as they can be: (i) expensive, (ii) potentially confer substantial health gains, but may be (iii) supported by a weak evidence base. The latter is usually characterized by a combination of earlier trials stratified effectively but often single arm and of insufficient duration to show the long-term benefits or harms that may accrue from the treatment decades down the line. These are key areas of uncertainty in the economic evaluation of these treatments.

The NICE/York study explored a hypothetical CAR T-cell therapy and analyzed how the NICE appraisal process is affected by various factors when assessing such a technology. Two treatment scenarios were considered: one looked at the treatment as a bridge to stem cell transplantation and the other used it with curative intent. The study set two hypothetical prices for this hypothetical product to use in health economic analyses. The prices were set in such a way that the health economic analyses would give results close to the cost–effectiveness thresholds used in NICE decision-making. Six different hypothetical evidence datasets were used – three for each 'indication' – to determine the impact of different levels of maturity in the evidence base. Within each set, cost–effectiveness analyses explored the impact of discounting rate (a method of reflecting the present value of the different costs and benefits of the treatment accruing over the time horizon of the analysis), price discounts and payment methods used.

The REGenableMED Policy Briefing suggested that the range of technologies studied should be extended to assess the suitability of available HTA methodologies in evaluating other types of regenerative medicines and cell therapies. It is clear that the hypothetical chimeric antigen receptor (CAR) T-cell therapy considered in the study was

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not representative of all such therapies; however, the lessons from this exercise are generalizable to a considerable extent to many technologies of this class. Another product priced similarly to the hypothetical prices used in the study, but offering only modest improvements to length and quality of life, may not be found to be cost-effective; but this would not be a deficiency in evaluation methods or the decision framework. The study illustrates the interplay between the estimated patient outcome benefits, uncertainty in those estimates and price and payment methods; the principles are widely applicable to diverse product types.

Overall the study found that NICE's methods and decision frameworks were broadly applicable to regenerative medicines and cell therapies, and highlighted areas for further consideration. For example, it stressed the need for improved quantification and presentation of clinical outcomes and decision uncertainty and the need to develop innovative payment methods to share the risk generated by this uncertainty. The implications of these issues will be explored further and, where appropriate, considered as part of the regular updates of the NICE Guide to the Methods of Technology Appraisal.

In order to deal with uncertainty in the evidence for potentially life-changing cell and gene therapies, to the point where payers are comfortable paying for these treatments, more intensive interaction between stakeholders might be helpful. In this context, recent initiatives such as the European Medicines Agency (EMA) Adaptive Pathways pilots and the NICE Office for Market Access (OMA) provide models where such interactions can take place in a 'safe harbor' environment. These early dialogues include regulators, HTA agencies, payers and patients and healthcare professional representatives. Such interactions support the design of optimal product development pathways including the managed introduction of technologies into clinical practice and exploring needs for appropriate post-authorization data collection. This latter approach is supported by the findings of the NICE/York study, which suggests that managed access agreements will sometimes be required to support reimbursement and that these may include a requirement for continued data collection.

The current UK Cancer Drugs Fund (CDF) is a managed access fund that allows for the collection of evidence to support a new cancer drug where there is insufficient evidence of clinical and/or cost–effectiveness to recommend it for routine commissioning but there is plausible promise that the technology could be cost-effective. The CDF managed access agreement will have two components: a data collection arrangement and CDF commercial agreement, which will allow for the drug to be funded for a fixed period of time while further evidence is collected. This approach may serve as a model that could be transferable to other expensive technologies with a limited evidence base. The CDF arrangements are also directly applicable to cell therapies and other advanced therapy medicinal products (ATMPs) addressing cancer indications.

Novel managed access agreements may include financial or research-based approaches. However, the costs of assessing the additional

evidence generated for the benefits and in implementing these schemes in order to make improved resource allocation decisions may add to the economic burden of the treatment. It is important that such approaches don't become the 'new norm' and that they are used selectively for treatments that appear to be transformational against unmet need and where major efforts to secure timely patient access are therefore needed.

So how can we combine licensing, evaluation and payment methods to ensure a sufficiently robust process to enable early adoption? What should managed access agreements look like for products that are expected to be transformative but where the long-term benefits, especially in comparison to current standard practice, have not been established?

Research-based approaches lend themselves to health technology assessment with the development of further evidence that will reduce uncertainty regarding long-term outcomes in a studied population of patients. Payment mechanisms that have been considered include: annuities, where the cost is spread across annual payments but the reimbursement decision has been made; lifetime leasing, which mitigates against real patient outcomes being less favorable than those estimated from limited trial data; and performance-based risk sharing schemes whereby, for example, costs related to product production are reimbursed at the willingness-to-pay level but further reimbursement is performance related through resource use/costs avoided and/or reimbursement related to delivery of clinical outcomes.

The existing methods, currently employed by NICE, to estimate the implications of uncertainty in the evidence for regenerative medicines and cell therapies and for how effective they may be in 'real life' settings may not be sufficient according to the York report. The report suggests additional methods, including innovative payment mechanisms such as those outlined above, use of individual patient data for small populations and exploring the scale of consequences for decision uncertainty as additional means of quantifying uncertainty.

A recent NICE Decision Support Unit (DSU) paper for Methods of Assessment of Managed Access was commissioned by NICE to identify potential approaches to managing the evaluation and funding of novel and high-cost healthcare interventions. The paper suggests a risk analysis framework for managed access agreements to help manage the risk associated with funding therapies that are providing innovative healthcare solutions for patients but where uncertainty is high. This DSU work will also be taken in to account by NICE through its processes for reviewing the methods of Technology Appraisal.

A key benefit of seeking early scientific advice, from an HTA perspective or a joint regulatory and HTA perspective, is in managing risks by informing developers about payer requirements for clinical and economic data collection. Mitigating uncertainty, in both monetary and health terms, through early advice helps avoid delays and potentially expensive mistakes in a product's development pathway, by ensuring the collection of the right data to support HTA as well as regulatory approval. NICE Scientific

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Advice, for example, advises companies directly and participates in parallel and joint advice with the EMA and MHRA, respectively. If developers take this early advice and minimize, as much as possible, the uncertainty in their data then payers can be more confident of what they are getting for their money.

While the study conducted by NICE and York showed that our health technology assessment processes were fundamentally applicable to cell and gene therapies, NICE is continuing to collaborate with other organizations to improve the path to patient access for these technologies. As previously mentioned, the NICE OMA has developed and hosts a multi-stakeholder 'safe harbor' that provides an infrastructure to help stakeholders explore the route to HTA evaluation within the UK healthcare landscape with advice from a dedicated team. OMA are also working with the MHRA, which has its own 'one-stop-shop' (the Regulatory Advice Service for Regenerative Medicine), which is hosted by the MHRA's Innovation Office and directly fields enquiries that span multiple regulatory agencies including the MHRA, Health Research Authority, HTA and the Human Fertilisation and Embryology Authority (HFEA).

NHS England and the Cell and Gene Therapy (CGT) Catapult are continuing to work together to improve the delivery of cell therapies to patients by addressing the technical problems in generating evidence for clinical efficacy, in response to recommendations in the RMEG report. NICE Scientific Advice has also developed and delivered seminars involving the CGT Catapult, MHRA and NHS England, exploring both HTA for cell and gene therapies and the barriers to adoption, which were very well received.

NHS England Specialised Commissioning has established a new directorate with a commercial focus. This directorate works on a number of innovative business models such as 'Commissioning through Evaluation', which enables a limited number of patients to access health technologies that are currently not routinely funded by the NHS. As with the CDF approach, the health technologies (mainly medical devices to date) should show significant promise clinically and be cost-effective before further data are collected within a formal evaluation program. These data will inform a final commissioning decision on the technology. Other recent approaches have included the creation of managed access agreements in collaboration with NICE for products that have undergone HST evaluation. The directorate includes a commercial negotiating team who are exploring a range of approaches that include an element of risk-sharing.

The collaborative approach by all these agencies in the UK aims to provide advice and help to the developers of cell and gene therapies, to navigate the hurdles in getting effective therapies to patients in a timely manner. We anticipate that the Accelerated Access Review in the UK will further strengthen the infrastructure to support timely patient access to transformational medicines.

In addition, EUNetHTA early dialogues provide a strategy to improve the quality and speed at which decisions regarding new therapies can be made by increasing understanding of available evidence

to HTA bodies and reimbursement bodies across Europe.

NICE has been involved in the EMA Adaptive Pathways pilot and participates in the Innovative Medicines Initiative (IMI) ADAPT-SMART project, which looks at tools and methodologies that could support adaptive pathways, including possible innovative clinical trial designs. Adaptive pathways seek to enable patient access to beneficial treatments for key patient groups at the earliest appropriate time in the product life span, which means that it is highly likely that less comprehensive data will be available when the product is being considered for reimbursement. It has been stipulated by the EMA and associated stakeholders that adaptive pathways do not change the standards for marketing authorization, meaning that sufficient evidence of a product's positive benefit–risk profile will still need to be demonstrated to achieve marketing authorization. In addition, adaptive pathways are not expected to become the standard development route for new products but will apply only to those products where standard regulatory pathways might not be sufficient in providing the earliest appropriate patient access.

The Innovative Medicines Initiative (IMI) GetReal project, in which NICE is involved, aims to show how robust methods of real-world evidence collection and synthesis could be adopted earlier in pharmaceutical research and development and the healthcare decision-making process. The overall goal is to have appropriate evidence available at the time of regulatory and HTA assessments to enable reliable estimates of effectiveness of new treatments in clinical practice. The increased understanding of health outcomes in routine clinical practice at the patient level can be synthesized into evidence from which conclusions can be drawn and funding decisions made. Moreover, evidence gathering and the development, following marketing authorization, of registries and real-world data that can provide supportive evidence will be key to increasing maturity in the evidence base for a technology.

In the UK, consideration needs to be given to the potential fall-out from the decision to leave the European Union on future research, regulatory, scientific and HTA collaboration across Europe. What will be the impact on regulation? What will be the impact on reference pricing? At the moment we just do not know.

CONCLUSION

The public wants effective medicines to reach patients as quickly and as safely as possible, especially where there is a high unmet need. For cell and gene therapies where the financial and clinical risks to cash-strapped health economies are huge, this is a major issue. It requires industry and healthcare system stakeholders to come together to develop innovative solutions to evidence generation and evaluation. It requires them to design practical payment methods to achieve a fair sharing of risk where accelerated access to therapies have left gaps or uncertainty in the evidence on which decisions need to be based.

NICE has done much to face and address the questions posed regarding efficacy and cost–effectiveness arising from the advent of cell and gene therapies and to try to find answers.

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The RMEG report and the response from NICE demonstrate that the healthcare system in the UK is prepared to address those difficult questions in an evidence-based way and has the capacity and drive to find workable solutions. This will ensure that these innovative therapies, with demonstrable life-changing benefits for patients, can be evaluated in a way that is fair for all stakeholders.

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