The assessment and appraisal of regenerative medicines and cell therapy products: an exploration of methods for review, economic evaluation and appraisal

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Scientific summary

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Background

Regenerative medicines replace or regenerate human cells, tissues or organs to restore or establish normal function. Potential breakthroughs in this area of clinical research are eagerly anticipated and expectations are often high because of the possibility of cures (or substantial improvements) for diseases that are currently deemed chronic or fatal. However, efficacy, safety and cost-effectiveness evaluations of regenerative medicines may be difficult compared with evaluations of conventional pharmaceutical treatments. The Regenerative Medicine Expert Group (RMEG) was tasked to develop a NHS regenerative medicine delivery readiness strategy and action plan. The RMEG requested an investigation to determine whether the conceptual differences between regenerative medicines and other types of health technology require different approaches to the assessment of efficacy, safety and cost-effectiveness.

Objectives

- To test the application of National Institute for Health and Care Excellence (NICE) appraisal methodology to regenerative medicines.
- To identify specific issues related to the appraisal of regenerative medicines using the current NICE appraisal process and decision framework.
- To develop a framework for those developing regenerative medicines to facilitate understanding of how NICE evaluates clinical effectiveness and cost-effectiveness.

Potential issues for the evaluation of clinical effectiveness

Two different approaches were taken to identify and explore issues and challenges that may be associated with NICE evaluations of regenerative medicines:

1. a broad exploration of the applicability of NICE technology appraisal (TA) methods to regenerative medicines
2. an exemplar NICE appraisal of a hypothetical regenerative medicine product.

Reviews were undertaken to identify and discuss TA methodology issues that may be particularly relevant to regenerative medicines: a review of European Medicines Agency (EMA), NICE and US Food and Drug Administration (FDA) assessments of regenerative medicines licensed in the European Union (EU); a review of the use of surrogate end points in clinical research; and a review of the biases likely to affect the results of non-randomised studies (NRSs) (with a particular focus on the challenges of using results from single-arm trials to estimate efficacy).

Several broad issues that may affect uncertainty were apparent from these reviews:

1. It was not universally the case that regenerative medicines are trialled using NRS designs.
2. With single-arm trials, a key consideration when judging levels of uncertainty should be the likelihood of cure or improvement *without* experimental treatment.
3. When single-arm trials or case series form the basis of a regulatory submission, the relative treatment effect generated is likely to be optimistic unless the historical control data are accurate.
4. When single-arm trial data are compared with historical data and adjustment for confounding is made, the selection of the method used must be explicit; despite advances in statistical techniques, challenges remain in generating accurate unbiased estimates of effect from non-randomised data.

5. Pivotal trials in regulatory submissions are likely to report surrogate primary end points. On average, trials using surrogates report larger treatment effects than trials using final patient-relevant outcomes. This has implications for effect estimate uncertainty, especially when *only* surrogate end points are reported. The choice of surrogate outcomes must be researched, explicit and justified, preferably through a systematic review. To maximise the use of *all* available data, and to reduce overall uncertainty, multivariate meta-analysis methods to analyse data should also be considered.
6. Use of intermediate shorter-term primary outcomes avoids the need for long follow-up but, when overall survival is a secondary outcome, data are immature at the point of regulatory approval.
7. The high technology status of regenerative medicines may imply greater potential for variation in response. This is likely to have implications in terms of the generalisability of efficacy and safety estimates obtained from small single-centre (probably expert-centre) studies, which may produce larger effect estimates than multicentre studies. In the absence of larger or more varied trials, this issue might be addressed only by access to individual patient data so that effect modifiers may be investigated.
8. The availability of confirmatory randomised controlled trials (RCTs) in a similar, larger population [e.g. B-cell acute lymphocytic (lymphoblastic) leukaemia (B-ALL) patients in *first* relapse] raises the possibility of incorporating indirectly relevant but more reliable (and possibly more mature) data into the analysis to reduce uncertainty; such data may become available as a result of the evolving regulatory pathways being developed by the EMA.
9. Most regenerative medicines are, by their nature, innovative products that may be subject to continuing development, with new generations of products having improved efficacy. This may pose problems when evaluating long-term efficacy and safety: to what extent can the long-term safety data from a first-generation product be used to inform the long-term safety of a related newly licensed second-generation product?

Potential issues for the evaluation of cost-effectiveness

Many of the issues associated with regenerative medicines will impact on the level of uncertainty associated with the cost-effectiveness of the technology when introduced into clinical practice. Even when products have a significant potential to confer important clinical advances over current therapies, this may not be known with a high level of certainty at the time of licensing the product. A new technology's cost-effectiveness may be more difficult to determine in these circumstances, and schemes or managed entry agreements (MEAs) that allow the development of further evidence or that entail a risk-sharing component may be required.

Several studies have concluded that reimbursement decisions and the possible use of MEAs should be based not only on the expected value of a technology but also on the value of further research, the anticipated effect of coverage on further research and the costs associated with reversing the decision. Importantly, provision already exists within NICE's *Guide to the Methods of Technology Appraisal* to accommodate some of these considerations. NICE will also need to consider whether further amendments to its processes and methods are required.

Exemplar National Institute for Health and Care Excellence appraisal of chimeric antigen receptor T-cells for relapsed/refractory B-cell acute lymphoblastic leukaemia

For the exemplar appraisal, the chosen hypothetical product was chimeric antigen receptor (CAR) T-cell therapy specific to the antigen CD (cluster of differentiation) 19 for treating relapsed (two relapses or more) or refractory B-ALL.

Clinical evidence for the efficacy and safety of chimeric antigen receptor T-cells for relapsed/refractory B-cell acute lymphoblastic leukaemia

The trial data for CAR T-cells are limited to small, single-arm studies. They have the potential to offer patients a 'bridge' to a stem cell transplant or possibly a cure (without transplant), depending on the type of CAR T-cell therapy. However, potentially serious adverse effects are possible. The relapsed/refractory B-ALL population is narrowly defined with extremely poor prognosis and limited therapy options. The length of persistence of CAR T-cells within patients has implications for both efficacy and safety; persistence needs to be long enough to eradicate malignant cells and short enough to prevent problematic B-cell aplasia. Length of persistence may dictate how CAR T-cells are used.

The target product profile and hypothetical evidence sets

Based on the available clinical evidence for CAR T-cell and licensed non-regenerative medicines for relapsed B-ALL, two target product profiles (TPPs) were developed:

1. CAR T-cell therapy used as a 'bridge to haematopoietic stem cell transplantation (HSCT)', in which the primary goal of treatment is to induce the short-term remission of disease to maximise the opportunity for successful HSCT
2. CAR T-cell therapy used with 'curative intent', in which the primary goal of treatment is long-term remission/cure of disease (with or without HSCT).

To explore the impact of different levels of precision and maturity in the evidence base, three hypothetical data sets were constructed for each TPP:

1. the minimum set (60–80 patients, median follow-up approximately 10 months) – the minimum data considered potentially sufficient for CAR T-cell therapy to be granted conditional regulatory approval
2. the intermediate set (60–80 patients, maximum follow-up 5 years) – a variant of the minimum set in which the efficacy and safety of CAR T-cell therapy has been assessed over a longer follow-up period
3. the mature set (120–140 patients, maximum follow-up 5 years) – a variant of the intermediate set in which the efficacy and safety of CAR T-cell therapy has been assessed in a larger clinical study but with a similar follow-up period as in the intermediate set.

Development of the exemplar cost-effectiveness model: summary of approach and key findings

Two de novo decision models were developed to assess the cost-effectiveness of CAR T-cell therapy within the two separate TPPs (bridge to HSCT and curative intent) across each of the separate evidence sets.

In the bridge to HSCT scenario, the primary health benefits of treatment with CAR T-cell therapy were assumed to be driven by an increase in the proportion of patients receiving HSCT and the subsequent success of HSCT itself. The introduction of an epidemiological 'link' between a potential established surrogate outcome/process and final health benefits [i.e. overall survival and quality-adjusted life-years (QALYs)] also enabled the use of external evidence to be utilised.

In the curative intent model, the assumption was that the CAR T-cell therapy potentially confers longer-term and potentially curative benefits without the need to bridge to HSCT. A simple three-state partitioned survival model was developed to model long-term outcomes through the direct extrapolation of overall survival data from the evidence sets.

Assumptions, strengths and limitations

A key assumption employed within both models was that, from year 5 onwards, all patients who remained alive experienced a mortality risk profile consistent with that of a long-term survivor of acute lymphocytic (lymphoblastic) leukaemia (ALL). Additional follow-up data could be used to test the validity of such an approach against any claims of longer-term mortality differences.

In the absence of a commercially available product and published price of CAR T-cell therapy, an assumption was made that the manufacturer would employ a value-based approach to its pricing, such that the resulting cost-effectiveness [incremental cost-effectiveness ratio (ICER)] estimate was close to NICE's cost-effectiveness threshold. In the context of the exemplar, this was assumed to be based on the maximum threshold assuming that the existing 'end-of-life' (EoL) criteria are met.

Assessment of cost-effectiveness, uncertainty and the value of alternative policy options: summary of approach and key findings

An important aspect of our work involved investigating how these estimates could inform the NICE TA process.

The sequence of assessments presented started with a conventional assessment of cost-effectiveness based on the current NICE reference case. Disaggregated estimates of the costs and outcomes were estimated, together with resulting cost-effectiveness estimates based on the ICER. These results were also expressed using net health effects (NHEs), representing the difference between any health gained with the intervention and health forgone elsewhere in the health-care system, expressed either in monetary or in QALY terms.

The impact of uncertainties was explored using conventional one-way sensitivity analyses and probabilistic approaches.

In addition to the analyses undertaken using the conventional reference case approaches, a series of more exploratory analyses were also undertaken. In particular, the per-patient assessments were scaled up to population assessments, requiring an estimate of the number of potentially eligible patients and an assessment of the period over which the therapy might be utilised within clinical practice.

The results of the population-based analyses were summarised in terms of incremental NHEs and the probability that CAR T-cell therapy was cost-effective. Alongside these more conventional assessments, an assessment of the scale of the likely consequences of uncertainty was considered to be potentially informative in relation to possible research recommendations. An estimate of the consequences of existing decision uncertainty was subsequently derived, reflecting the potential magnitude of NHEs that could be gained if uncertainty surrounding this decision could be resolved immediately.

Impact of alternative pricing scenarios

Using the different analyses, the impact of alternative pricing scenarios was explored, including a fixed price reduction as well as more sophisticated schemes based on pay for performance and leasing approaches. Similarly, the impact of the alternative evidence sets was explored to establish the implications of the increased precision and maturity assumed in the intermediate and mature evidence sets.

Quantifying potential uncertainties

An important consideration within this work is the extent to which current NICE methods and processes are likely to appropriately quantify the potential uncertainties surrounding regenerative medicines and cell-based therapies to ensure that appropriate policy decisions are made regarding potentially promising technologies. Our findings show that the conventional assessments requested within the current TA process may not be sufficient. Estimates of the ICER and associated probabilities that CAR T-cell therapy is cost-effective at a specific threshold were shown to be virtually identical in one of the TPPs despite being based on three different evidence sets with varying levels of precision and maturity. Similarly, across both TPPs, several of the alternative pricing schemes again reported similar estimates of the ICER and associated probabilities that CAR T-cell therapy is cost-effective. Consequently, it is unclear how these differences would be reflected within the current TA process.

Consideration of the scale of the consequences for population NHEs provides a clearer distinction between the different evidence sets and an assessment of the impact of alternative pricing schemes. Consequently, their more routine application within the TA process for regenerative and cell-based therapies may be an important consideration for future processes. Such information might provide an important basis for

discussions between manufacturers, NICE and other relevant parties in terms of how the existing uncertainties might be appropriately managed, ensuring that risks and benefits are more appropriately shared.

Issues arising from the National Institute for Health and Care Excellence panel meeting

A separate panel and meeting were convened by NICE to discuss the findings of the exemplar appraisal, assess the clinical effectiveness and cost-effectiveness evidence informing the separate TPPs and identify potential issues and challenges for the NICE TA appraisal process and methods. A summary of the clinical effectiveness and cost-effectiveness evidence was presented to the panel, who were asked to deliberate on the range of scenarios and to provide 'hypothetical' decisions and outline the main considerations for these.

The key consideration relating to the clinical effectiveness evidence was how decisions can be made for technologies that look highly promising but for which the evidence base is highly uncertain, at a potentially high but actually unknown risk of bias and which are extremely immature. As appraisals of regenerative medicines are likely to be conducted in the context of conditional regulatory approval, the panel considered that it would be important to know what research had been mandated by the regulator and hence what uncertainty could reasonably be expected to be resolved in the near future. There was concern regarding the difficulty of decommissioning services following (what later proved to be) incorrect recommendations.

A key consideration regarding the cost-effectiveness results and implications for the 'hypothetical' decisions was whether the panel considered that existing criteria considered within the TA process in relation to EoL could be applied. The panel accepted that the exemplar met the requirements of the EoL criteria but concluded that other considerations (e.g. innovation) would not be applied in addition.

The panel raised issues regarding the possible nature and magnitude of any irrecoverable costs that might be incurred by the NHS and the implications for its decisions. The panel acknowledged that the different pricing schemes had important impacts both in terms of the ICER and in terms of the allocation of any risk between the NHS and manufacturers. The concept of the 'leasing approach' was identified as a potentially important option.

The panel acknowledged the challenges and difficulties of generating mature evidence at the point at which a product is launched. In particular, the panel noted that a comparison of the magnitude of the incremental NHEs and the consequences of decision uncertainty provided an important starting point for deliberations in considering the scale of the NHEs that could be achieved by immediate approval and that which might be achieved by further research.

Summary conclusions

Our research found that the clinical evidence about regenerative medicines is expected to be associated with much uncertainty. Existing methods are available to adjust for and minimise the risk of bias and uncertainty in data analyses. Although there will be a significant level of uncertainty in determining the long-term costs and benefits to patients and the NHS, the existing methods available to estimate the implications of this uncertainty are sufficient. The use of risk-sharing agreements between the NHS and manufacturers of regenerative medicines should be investigated further.

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