Exploring the assessment and appraisal of regenerative medicines and cell therapy products

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Authors Nick Crabb, Programme Director, Scientific Affairs
Andrew Stevens, Technology Appraisals Committee Chair

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Executive Summary

1. This paper presents an overview of a project designed to test whether the NICE health technology appraisal methods and processes are fit for purpose for regenerative medicines and cell therapies. The relatively new field of Regenerative Medicine is potentially important to both the UK economy and to the health of some patients. However, it is has been suggested that these types of technologies present special difficulties for NICE's technology appraisal because regenerative medicines and cell therapies can be: (i) expensive per patient, (ii) be supported by a weak evidence base, but (iii) potentially confer substantial health gains.

2. To test the application of NICE appraisal methodology to regenerative medicines and cell therapies, a special NICE study and Expert Panel was set up to consider CAR (chimeric antigen receptor) T-cell therapy in relapsed or refractory B-cell acute lymphoblastic leukaemia in children and young adults. CAR T-cell therapy is a real but as yet unlicensed therapy at the early stages of development with sparse data (two very small single-arm trials) and an unknown price.

3. The University of York provided an assessment report using a hypothetical, more advanced (but realistic) data set for CAR T-Cell therapy both (1) as a bridge to stem cell transplantation, and (2) with curative intent. They also set two theoretical prices for the technology to use in a health economic analysis that pushed the experimental appraisal right to the limit at which NICE would be likely to reject the technologies. The prices and gains examined were £350,000 and 7.5 QALY for the bridge indication; and over £500,000 and 10 QALYs for the curative intent indication per patient. The York team also provided additional more mature hypothetical data sets and alternative means of product pricing for the Expert Panel to explore.

   The overall findings 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.

Introduction

4. Regenerative medicines replace or regenerate human cells, tissues or organs to restore or establish normal function.

5. In response to a recommendation by the Regenerative Medicine Expert Group (appendix 3), NICE, in collaboration with the Centre for Reviews and Dissemination/Centre for Health Economics, University of York (the York team), has undertaken a study exploring the assessment and appraisal of regenerative medicines and cell therapy products. A detailed technical report has been produced by the York team and is available from the NICE website. This short overview outlines the background leading to the study, the study objectives and design, and conclusions and implications. Recommendations for further work are also made.

Background

6. Following the House of Lords Regenerative Medicine Inquiry, the Department of Health (DH) established the Regenerative Medicine Expert Group (RMEG). Throughout 2014, RMEG worked on an NHS regenerative medicine readiness strategy and assessed the effect of regulation on the development of regenerative medicines in the UK. NICE was represented on RMEG and also on a sub-group on Evaluation and Commissioning. The RMEG membership is shown in appendix 3.

7. The Evaluation and Commissioning Subgroup comprised representation from NICE, NHS England, regenerative medicine companies, clinicians, patient organisations, academics and the Cell and Gene Therapy Catapult. Within the subgroup, there were differing views on whether NICE methods and decision frameworks were fit for purpose for the assessment and appraisal of regenerative medicines. The consensus was that key features and benefits of regenerative medicines may be captured within current NICE appraisal methods but there were, nonetheless, major concerns that regenerative medicines could be particularly difficult to assess, that cost effectiveness thresholds may be challenging given the high cost of goods and that NICE appraisal could be a block to patient access and clinical adoption.

8. The RMEG subgroup therefore recommended that an **exploratory study of the appraisal of example regenerative medicine products** be commissioned and published by NICE to highlight key issues in the evaluation of regenerative medicines and explore the suitability (or otherwise) of current methods. The subgroup further recommended that the exercise should be designed to add to the learning emerging from actual appraisals of regenerative medicines. The subgroup recommendation was strongly endorsed by the RMEG Chair and members.

9. A study outline was subsequently developed and agreed with subgroup members and the RMEG. The Centre for Reviews and Dissemination/Centre for

Health Economics, University of York was assigned to this project through a commission by the NIHR HTA Programme.

10. The NICE Board approved the study in December 2014, a report from the RMEG detailing its findings and recommendations was published in March 2015 and NICE and the York team commenced the study in April 2015.

Study Objectives and Design

11. The study objectives were:

    - To test the application of NICE appraisal methodology to regenerative medicines and cell therapies, identifying challenges and any areas where methods research and/or adaptation of methodology is appropriate

    - To identify specific issues related to the appraisal of regenerative medicines and cell therapies using the current NICE appraisal process and decision framework

    - To develop a framework for those developing regenerative medicines and cell therapies to facilitate understanding of how NICE evaluates clinical and cost effectiveness and to identify the most important evidence areas to develop before cost-effectiveness can be reasonably estimated.

12. A Project Advisory Group (see appendix 1) was recruited in collaboration with the DH RMEG secretariat. Members were mainly drawn from the RMEG evaluation and commissioning subgroup. This group had one formal meeting and supported the York team in the preparation of the detailed study protocol. Members of the group provided ad-hoc support to the York team throughout the study. Project Advisory Group members also provided feedback on draft documents prior to publication, having signed confidentiality agreements.

13. The study protocol was published on the NICE website (https://www.nice.org.uk/about/what-we-do/science-policy-research/nice-research). Much of the study concerned a hypothetical example product with characteristics based on early clinical data for related real products supplemented with hypothetical evidence.

14. The chosen example product was CAR (chimeric antigen receptor) T-cell therapy specific to antigen CD19, for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (B-ALL) in children and young adults. This combination was selected because of the existence of relatively mature data from academic trials (none of the currently available CAR T-cell products are licensed). Based on the available clinical evidence, two target product profiles (TPPs) were developed, reflecting the potential uses of CAR T-cell products in the B-ALL care pathway:

    - CAR T-cell therapy used “as a bridge” to hematopoietic stem cell transplantation (HSCT), where the primary goal of treatment is to induce short-term remission of disease in order to maximise the opportunity for HSCT.

- CAR T-cell therapy used with “curative intent” where the primary goal of treatment is long-term remission / cure (with or without HSCT)

15. These two approaches to treatment with CAR T-cell therapy imply two different contexts in which the therapy may be evaluated requiring consideration as two distinct scenarios.

16. To explore the impact of different levels of maturity in the evidence base, three hypothetical evidence sets were constructed for each target product profile:

    - The minimum set (60-80 patients, median follow-up approx. 10 months): the minimum data considered potentially sufficient for CAR T-cell therapy to be granted conditional regulatory approval.

    - The intermediate set (60-80 patients, maximum follow-up of 5 years): a variant of the minimum set, where the efficacy and safety of CAR T-cell therapy has been assessed over a longer follow-up period.

    - The mature set (120-140 patients, maximum follow-up of 5 years): a variant of the intermediate set where 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 the intermediate set.

17. None of the clinical studies used in devising the target product profiles and evidence sets included control groups; so “historical” controls were used.

18. The two target product profiles together with the three hypothetical evidence sets provided six evidence scenarios that were considered in the study.

19. In modelling cost-effectiveness, an estimate of the acquisition cost of CAR T-cell therapy was needed. In the absence of a commercially available product and published price, a price was assumed such that the economic analysis would give a result close to NICE’s cost effectiveness threshold. In the context of the examples, it was determined that the existing “end of life” criteria are met where a QALY weighting equivalent to an appraisal threshold of £50,000 per QALY applies. ***Importantly, this price is not considered to be indicative of the acquisition costs that might be set when commercial products are available.*** It is also important to note that the “end of life” criteria will not apply to all regenerative medicines. Normally a cost per QALY under £20,000 - £30,000 would be required for a NICE Appraisal Committee to consider a product cost effective.

20. Within each of the six evidence sets, cost effectiveness analyses explored the impact of price discounts, payment models and discounting rate used in the economic analyses.

21. An Expert Panel (see appendix 2) with a strong understanding of NICE Technology Appraisals was recruited. A meeting of this panel was held to consider the scenarios from the York study and for each scenario the panel was asked to:

- Indicate the decision that would most likely be made by a TA Committee if the scenario was encountered in a real appraisal

- Highlight any difficulties in reaching the decision, especially where the difficulties are not commonly encountered for other product types

- Highlight any issues related to methods or decision frameworks and potential solutions that could address the difficulties encountered

22. The ability to probe multiple scenarios was to provide insights into methodology issues connected with regenerative medicine product characteristics, pricing and funding models and evidence maturity. It is important to note, however, that it was difficult to identify an example that would be representative of all the complexities associated with regenerative medicines and cell therapies. The York team therefore proposed that in addition to the exploration of the example product scenarios, the study be extended to include learning from "real" appraisals of regenerative medicines and potentially a broader range of products. This was to make the overall learning from the study more generalizable and useful across regenerative medicine and cell therapy product types. This proposal was strongly supported and is reflected in the study protocol. Consequently, two different approaches were taken by the York team to identify and explore issues and challenges which may be associated with NICE evaluations of regenerative medicines:

    - A broad exploration of the applicability of NICE technology appraisals (TA) methods to regenerative medicines and cell therapies.

    - Detailed investigation of the hypothetical examples highlighted above

23. The York team produced a detailed assessment report to inform the Expert Panel meeting and then produced a final report that included the outcomes and commentary from the Panel consideration of the scenarios presented. This report is independent of NICE and subject to National Institute for Health Research (NIHR) review and governance processes. NICE participants in the project reviewed draft versions and provided feedback to the York team. In addition to the version on the NICE website, a final report will be produced and published as part of the HTA Monograph Series (http://www.journalslibrary.nihr.ac.uk/hta).

24. The independent York report is considered the major deliverable from the study and is expected to be a key resource to many regenerative medicine and cell therapy stakeholders.

Study Outcomes

25. The York study includes extensive review of the literature, analyses and commentary. Some of the key findings, especially those with potential policy implications, are briefly outlined below.

Broad Exploration of the Applicability of NICE TA Methods

26. Several pragmatic (not systematic) reviews were undertaken by the York team to identify technology appraisal methods issues which may be particularly relevant to regenerative medicines. These included a review of NICE, EMA and FDA assessments of regenerative medicines licensed in the UK, a review of the use of surrogate outcomes in clinical research, and a review of the biases likely to affect the results of non-randomised studies (with a particular focus on the challenges of using results from single-arm trials to estimate efficacy). A pragmatic review of potential cost-effectiveness issues to identify possible conceptual differences between regenerative medicines and more conventional medicines was also undertaken. This included a review of the appraisals of regenerative medicine products undertaken by NICE. Autologous chondrocyte implantation (ACI) for the treatment of cartilage defects in the knee joints was first appraised by NICE in 2005 (TA89) and this is currently being reviewed (ID686). The appraisal of sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer was also reviewed. Published as TA332 in February 2015, the appraisal was withdrawn due to the marketing authorisation being withdrawn in May 2015.

    The findings are discussed extensively in the York report.

Hypothetical Examples

The Target Product Profiles (TPPs)

27. Target product profiles based on the limited and early evidence available were produced by the York team. These profiles capture the characteristics of hypothetical example products. Whilst clearly hypothetical, the link with the early clinical evidence means that there is some foundation to the target product profiles generated. An approach was used to determine the hypothetical price of the product such that economic analysis would give a result close to NICE's cost effectiveness threshold. Consequently the price is based on the assumed clinical performance and outcomes – which differ for the two target product profiles. The hypothetical patient outcomes and base case price were determined as:

Table 1 – Benefits and Costs of the 2 Target Product Profiles

	Bridge to HSCT TPP	Curative Intent TPP
Assumed Individual patient level Incremental QALY gain	7.46	10.07
Assumed Price (acquisition cost of the therapy)	£356.100	£528,600

28. It is important to note that products with the characteristics of these target product profiles would represent major advances in therapy, offering profound benefits to eligible patients compared with the current NHS standard of care. 10 QALYs, for example, represent a 10 year life extension at full health. Step-

change improvements in patient outcomes from cancer treatments of this magnitude are rarely seen with conventional therapies.

Analysis and Presentation of Uncertainty

29. Although the product characteristics captured in the target product profiles represent the potential for profound patient benefits, there is also very high uncertainty around the actual levels of benefit that these products would deliver given the assumptions that need to be made to extrapolate from small single-arm trials to long term patient outcomes. Methodological considerations explored by the York team, including approaches for minimising bias from the use of single-arm studies and historical controls, are comprehensively covered in the York report. Even with the application of best methodology, there is inevitably a high level of uncertainty associated with outcome estimates from such early single-arm studies.

30. To probe the impact of evidence maturity the three hypothetical evidence sets were developed. The minimum evidence set was designed to represent the minimum evidence that would likely be available for a therapy to receive conditional regulatory approval. This minimum evidence set was considered particularly important as it represents the greatest challenge to those responsible for health technology assessment and associated decision making.

31. The York report highlights the importance of analysing and representing uncertainty when considering products that are very promising, expensive and where the evidence is immature. Uncertainty around the actual length and quality of life benefits to patients results in uncertainty in cost effectiveness analyses and decision uncertainty. The York work included developing a framework for considering uncertainty and this was explored further with the Expert Panel. The Panel found the York framework very informative and concluded that the careful exploration of uncertainty was essential to appropriate decision making in these circumstances. Detailed commentary on the analysis and presentation of uncertainty is available from Section 9 of the York report.

32. In presenting the scenarios to the Expert Panel, the York team included the parameters normally considered by NICE Appraisal Committees. These included central estimates of Incremental Cost Effectiveness Ratios (ICER) – the cost per QALY compared to the current standard of care, sensitivity analyses to probe the impact of variation in economic model assumptions, and the probability of the therapy being cost effective.

33. In addition, the York team modelled and presented population level Incremental Net Health Effect (NHE). This considers the impact of recommending the therapy on population level health based on the cost effectiveness threshold used in decision making. Where the ICER is above the threshold and the therapy therefore not considered cost effective, NHE is negative – overall more health gain could be achieved at population level by not funding the therapy and instead investing the resources in more cost effective treatments and interventions. Conversely, ICER estimates below the threshold result in positive NHE. NHE may be expressed in terms of QALYs or financially.

34. The York Team also assessed the scale of the likely consequences of decision uncertainty, reflecting the potential magnitude of NHEs that could be gained if uncertainty surrounding potential decisions could be resolved. These were also expressed in terms of QALYs and costs. Tables 2 and 3 below show population NHE and uncertainty values based on an estimated patient population of 38 patients per year over a 10 year period for each of the target product profiles (ICERs are the same at an individual or population level).

35. It is important to note that this novel framework for quantifying and presenting decision uncertainty is not routinely used in NICE Technology Appraisals, nor is it yet a widely accepted approach. It was developed by the York team for this project to reflect the combination of very high expected patient benefits and very high decision uncertainty where decision making is particularly challenging.

Expert Panel Consideration of Scenarios

Bridge to HSCT Target Product Profile (minimum evidence set)

Table 2 – Outcomes of Bridge to HSTC Target Product Profile (minimum evidence set)

Scenario	ICER	Incremental NHE QALY (£)	Probability Cost Effective	Consequences of decision uncertainty QALY (£)	Expert Panel "Decision"
Base case (£356,100 one-off acquisition cost per patient)	£55,090	-216 (-£10,794,902)	26.1%	56.3 (£2,813,197)	No
Discount of 20% on base case acquisition cost (£320,490 per patient)	£44,336	241 (£12,067,402)	76.5%	47.3 (£2,365,835)	Borderline
Lifetime leasing method (£2,756 per month)	£54,227	-180 (-£8,997,139)	22.1%	22.5 (£1,123,900)	No
Payment for patients with remission only (approx. 35% reduction in average cost per patient)	£36,430	577 (£28,861,808)	96.8%	3.9 (£195,152)	Yes
Additional scenario modelled by the York team after the Expert Panel meeting					
Discount of 20% on base case with Lifetime Leasing (£2,205 per month)	£44,015	252 (£12,624,164)	87.4%	19.0 (£948,311)	Assumed Borderline/Yes

36. The Expert Panel did not consider the base case ICER to be supportable. It was above the applicable threshold resulting in a net loss in population health taking the wider NHS into account. The 20% discount scenario resulted in an ICER below the applicable threshold, but the panel expressed significant concerns around the decision uncertainty and considered that this scenario was

borderline. Table 2 shows that the “uncertainty QALYs” are around 20% of the possible gain (47.3 and 241 respectively). In these circumstances the Expert Panel concluded that a higher level of discount would offset the uncertainty and would be a mechanism for increasing the likelihood of a positive decision.

37. The lifetime leasing method of payment was viewed with considerable interest by the Panel. The actual scenario presented was not considered supportable. The lifetime leasing method, where a monthly fee is paid for the duration of treatment benefits (until death) greatly reduces the decision uncertainty. The term “leasing” normally refers to payment for the continued use of an asset. It is important to note that in the context of the lifetime leasing method considered here, the asset in question is the health gain delivered rather than the CAR T-cell therapy itself. Full details of a lifetime leasing payment model were not presented to the Panel but the clear view was that such methodological approaches should be developed. The Panel considered that practical, workable payment methodologies based on the lifetime leasing method could be very important in managing decision uncertainty and in facilitating early patient access while the evidence was immature. The Panel indicated that a combination of a 20% discount on the base case costs and lifetime leasing method would most likely be viewed favourably. This scenario was modelled by the York team following the Expert Panel meeting and is presented in Table 2.

38. Another outcomes-based payment model, where payment is made only for patients with remission was also included in the York study and considered by the Expert Panel. Based on the model assumptions, this would result in a reduction of approx. 35% in the average treatment cost per patient compared to the base case. This significantly reduces the ICER and reduces decision uncertainty to a very low level. Assuming a practical, workable payment system could be devised, the Panel concluded that this scenario would be considered favourably.

39. A key issue considered in the York report and discussed by the Expert Panel was the discount rate that should be applied. Discounting is widely applied in the economic evaluations of goods, including health technologies, and discounting values future benefits and costs less than those that occur in the present. In the base case, the normal discounting rate of 3.5% was applied to both benefits and costs. Discounting disproportionately impacts the benefits of therapies with high upfront costs but benefits delivered over a prolonged period. Currently, when these conditions arise, there is the provision in NICE methods for 1.5% discounting to be applied where defined criteria are met (section 6.2.19 of the NICE Guide to the Methods of Technology Appraisal, 2013):

    - In cases where treatment restores people who would otherwise die or have a very severely impaired life to full or near full health, and when this is sustained over a very long period (normally at least 30 years), cost-effectiveness analyses are very sensitive to the discount rate used. In this circumstance, analyses that use a non-reference case discount rate for costs and outcomes may be considered. A discount rate of 1.5% for costs and benefits may be considered by the Appraisal Committee if it is highly likely that, on the basis of the evidence presented, the long term health benefits will be achieved.

Further, the Appraisal Committee will need to be satisfied that the introduction of the technology does not commit the NHS to significant irrecoverable costs.

40. The Panel considered that CAR T-cell therapy would not meet these criteria as currently written. In particular, the Panel considered that the introduction of the example products could commit the NHS to significant irrecoverable costs and it could not be determined at the time of the initial decision whether the long term health benefits would be achieved. Consequently the Panel considered that they could not apply 1.5% discounting. They recognised that NICE's existing methods are vulnerable to the overuse of this discounting variant. They did, however, consider that the target product profiles presented for CAR T-cell therapy represented a situation where the scale of the benefits could be transformative for patients and because they were delivered over a prolonged period, application of a lower discounting rate warranted further consideration. It was noted that 1.5% discounting reduced the ICER relative to the base case by 30%.

Bridge to HSCT Target Product Profile (intermediate and mature evidence sets)

41. For this target product profile, increasing maturity of evidence had relatively low impact on the probability of therapy being cost effective or the consequences of decision uncertainty. The key outcome from the CAR T-cell therapy in this example is clinical remission that can be estimated with reasonable accuracy from even the minimum evidence set.

Curative Intent Target Product Profile (minimum evidence set)

Table 3: Outcomes from Curative Intent Target Product Profile (minimum evidence set)

Scenario	ICER	Incremental NHE QALY (£)	Probability Cost Effective	Consequences of decision uncertainty QALY (£)	Expert Panel "Decision"
Scenarios reviewed by the Expert Panel					
Base case (£528,600 one-off acquisition cost per patient)	£50,906	-56 (-£2,902,629)	50.7%	304.6 (£15,229,786)	No
Discount of 10% on base case acquisition cost (£475,740 per patient)	£45,131	306 (£15,293,860)	64.2%	209.1 (£10,456,541)	Borderline/No
Lifetime leasing method (£3,283 per month)	£50,618	-38 (-£1,910,653)	49.2%	65.6 (£3,227,969)	No
Payment for patients with remission only (approx.10% reduction in average cost per patient)	£45,708	267 (£13,325,042)	63.9%	236.1 (£11,803,131)	Borderline/No
Additional scenarios modelled by the York team after the Expert Panel meeting					
Discount of 10% on base case price with lifetime leasing (£2,955 per month)	£45,502	275 (£13,750,033)	87.2%	27.2 (£1,358,584)	*Assumed Borderline/Yes*
Same pricing as bridging to HSCT TPP (£356,100 per patient)	£34,337	951 (£47,555,583)	85.6%	73.1 (£3,655,876)	*Assumed Yes*
Same total cost as bridging TPP with lifetime leasing (£2,221 per month)	£33,277	1050 (£52,500,851)	99.4%	2.3 (£112,597)	*Assumed Yes*
Same total cost as bridging TPP with lifetime leasing and 10% discount (£1,990 per month)	£29,713	1262.40 (£63,120,093)	100%	0 (£0)	*Assumed Yes*

42. For this target product profile, where CAR T-cell therapy is being used with curative intent and not as a bridge to an established therapy, cost effectiveness estimates are very dependent on extrapolation from the available evidence. As a

consequence the decision uncertainty is considerably higher than reported for the Bridge to HSCT target product profile. The approach to determining a hypothetical price of CAR T-cell therapy (such that the economic analysis would give a result close to NICE's cost effectiveness threshold) resulted in the base case price being substantially higher for the curative intent target product profile than for the bridge to HSCT target product profile.

43. The Expert Panel considered that decision uncertainty was a major factor in "decision making" around the scenarios presented. The base case was not considered supportable as the ICER was above the threshold and the decision uncertainty was high. Although a 10% discount in the acquisition cost resulted in an ICER below the threshold, the decision uncertainty was still very high (much higher than for any of the scenarios presented for the bridge to HSCT target product profile) and high in proportion to the potential health gain (209.1 and 306 QALY respectively in Table 3). The Expert Panel considered this scenario to be borderline – and probably not supportable given the decision uncertainty. The Panel considered that a higher level of discount on costs would be a mechanism for increasing the likelihood of a positive decision.

44. As for the Bridge to HSCT target product profile, the lifetime leasing method of payment was viewed with considerable interest by the panel. Although the actual scenario presented was not considered supportable, the decision uncertainty, although it remained relatively high, was substantially reduced compared to the base case. The Expert Panel considered that a lifetime leasing model combined with an ICER safely under the threshold (e.g. a scenario combining the 10% discount and lifetime leasing method) would reduce both the ICER and decision uncertainty to acceptable levels and would most likely be viewed favourably if such payment systems were available and supported as practical and workable in the NHS. This scenario was modelled by the York team following the Expert Panel meeting and is included in Table 3.

45. A model where payment is made only for patients with remission was also considered for this target product profile. In this case, due to anticipated lower rates of failing to achieve remission, this would result in a reduction of around 10% in the average cost per patient compared to the base case. The resulting ICER is below the relevant threshold but decision uncertainty is still very high. The Expert Panel considered this scenario to be borderline – and probably not supportable given the decision uncertainty.

46. During the Panel deliberations, it was commented that a lower costs of the technologies would make decisions easier. For example, the price used in the Bridge to HSCT target product profile (£356,100 per patient) would greatly simplify decision making around the Curative Intent target product profile. In response to this, the York Team modelled three additional scenarios shown in Table 3. Although the Panel did not specifically consider these scenarios, from their deliberations, it is reasonable to assume that all of these scenarios would have been viewed favourably.

47. It is important to note that the curative intent target product profile with the minimum evidence set represents an extreme case of great therapeutic potential combined with very high uncertainty – a very challenging combination for those

responsible for making best use of limited healthcare resources. These scenarios help to explore how both price and payment methods impact estimates of cost-effectiveness and decision uncertainty.

48. The impact of discounting rates was also modelled for the Curative Intent target product profile. It was noted that 1.5% discounting reduced the ICER relative to the base case by 29%.

Curative Intent Target Product Profile (intermediate and mature evidence sets)

Table 4: Outcomes from Curative Intent Target Product Profile (intermediate and mature evidence sets)

Scenario	ICER	Incremental NHE QALY (£)	Probability Cost Effective	Consequences of decision uncertainty QALY (£)	Expert Panel "Decision"
Base case (minimum evidence set)	£50,906	-56 (-£2,902,629)	50.7%	304.6 (£15,229,786)	No
Intermediate evidence set	£43,344	486 (£24,311,227)	85.9%	40.6 (£2,031,623)	Borderline
Mature evidence set	£43,252	495 (£24,723,328)	91.5%	14.1 (£707,136)	Borderline/Yes

49. For this target product profile, the increased maturity of evidence has a significant impact on the assumption that additional evidence increases the certainty about the curative benefits of treatment. There is also greater certainty in the cost effectiveness of the treatment and a significant decrease in overall decision uncertainty. The Expert Panel considered that the intermediate and mature data set scenarios above were potentially supportable as indicated in Table 4.

Conclusions and Implications

50. It is clear from the Panel consideration of the hypothetical example products that the methodology and decision framework of NICE Technology Appraisals is fundamentally applicable to regenerative medicines and cell therapies. The high treatment costs being considered cost effective were due to the major increases in patient outcome benefits represented by the example target product profiles. Clearly, in cases where products offer modest improvements in patient outcomes, high prices such as those of the examples would not be considered cost effective. Because the NICE Technology Appraisals decision framework is value based with cost effectiveness directly linked to the incremental improvements in patient outcomes, this incentivises the development of innovative medicines addressing high unmet need.

51. One of the major challenges encountered in the study was how to deal with uncertainty. The Curative Intent target product profile in particular, represented

an extreme case where the projected benefits to patients were very great (around 10 QALY per patient) but combined with a very high level of uncertainty. The scenarios developed and considered by the Expert Panel demonstrated that innovative payment methods, such as the lifetime leasing, may have a key role to play in managing and sharing the financial risk.

52. In the case of the Curative Intent target product profile, increased maturity of the evidence had a significant impact on reducing uncertainty so where mature evidence is available, conventional one-off payments for products may be sustainable.

53. Given the importance of understanding and managing uncertainty, the Expert Panel highlighted the need to further develop ways in which uncertainty can be quantified and presented to decision makers. NICE is likely to increasingly encounter situations where high promise is combined with immature evidence and robust approaches to understanding and managing uncertainty are needed.

54. NICE, through its normal processes for reviewing the methods of Technology Appraisal, has initiated work on the quantification of decision uncertainty outside of this regenerative medicine study.

55. A further potential consideration from the study is the discounting rate that should be applied to the costs and benefits of these types of technologies. The example target product profiles are cases where high upfront costs are followed by benefits delivered over a prolonged period of time and where higher discounting rates disproportionately impact the benefits. There is the provision in NICE methods for exceptionally applying a 1.5% discounting rate to costs and benefits where specified criteria are met (see above). The example target product profiles were not considered to meet these criteria as currently written.

Recommendations

- It is recommended that NICE informs interested parties that the Technology Appraisals framework is applicable to regenerative medicines and cell therapy technologies comparable to the target product profiles considered in this study.

- It is recommended that NICE continues to further develop the ways in which uncertainty can be quantified and presented to decision makers taking account of the framework developed by the York Team.

- It is recommended that NICE collaborates with other stakeholders (e.g. DH, NHS England, Industry, Cell and Gene Therapy Catapult) to develop practical payment methods for managing and sharing financial risk, such as lifetime leasing.

- It is recommended that NICE takes account of this study when reviewing the criteria for when the 1.5% discounting rate should be applied.

Appendix1- Project Advisory Group (PAG)

PAG Members and Specialist Clinical Advisers to the Expert Panel

Natalie Mount	Chief Clinical Officer, Cell and Gene Therapy Catapult
Robert Hawkins	Professor of Medical Oncology, University of Manchester

PAG Members

Andrew Stevens (Chair)	Chair of NICE Technology Appraisals Committee C
Ian McKay	Senior Scientific Officer, Genomics Science and Emerging Therapies, Department of Health
Panos Kefalas	Head of Health Economics and Market Access, Cell and Gene Therapy Catapult
Matthew Taylor	Director York Health Economics Consortium, University of York
Philip Newsome	Professor of Experimental Hepatology, University of Birmingham
Chris Mason	Professor of Regenerative Medicine Bioprocessing, University college London
Angela Blake	Head of Health & Value, Pfizer UK
Andrew Webster	Director of the Science and Technology Studies Unit, University of York
Paul Catchpole	Director of Value and Access, ABPI
Michael Hunt	Chief Financial Officer, ReNeuron
Siobhan Connor	Clinical Effectiveness Executive, BUPA
Holger Mueller	Senior VP, Commercial Operations, Cell Medica
Ahmed Syed	Clinical Effectiveness Team, Specialised Services, NHS England
Claude Schmitt	Head of Market Access, Rare Diseases, GSK
Angela Crossman	Global Market Access Director, Gene Therapy, GSK
Helen Tayton-Martin	Chief Operating Officer, Adaptimmune
Matthew Durdy	Chief Business Officer , Cell and Gene Therapy Catapult

Appendix 2 – Expert Panel

Andrew Stevens (Chair)	NICE Technology Appraisals Committee Chair
Peter Jackson	Consultant Physician & Hon. Reader in Clinical Pharmacology and Therapeutics, Sheffield Teaching Hospitals
Gary McVeigh	Professor of Cardiovascular Medicine, Queen's University Belfast and Consultant Physician, Belfast Health and Social Care Trust
Peter Selby	Consultant Physician, Central Manchester University Hospitals NHS Foundation Trust
Jonathan Michaels	Hon. Professor of Clinical Decision Science, University of Sheffield
Mark Sculpher	Professor of Health Economics, University of York
Allan Wailoo	Professor of Health Economics & Director of NICE Decision Support Unit, University of Sheffield
John Cairns	Professor of Health Economics Public Health and Policy, London School of Hygiene and Tropical Medicine
Norman Waugh	Professor in Public Health, Warwick Medical School
Paul Miller	Director, Payer Evidence, AstraZeneca
Chris O'Regan	Head of Health Technology and Outcomes Research, Merck Sharp & Dohme
Danielle Preedy	Assistant Director , NIHR Evaluation, Trials and Studies Coordinating Centre
David Chandler	Chief Executive of the Psoriasis and Psoriatic Arthritis Alliance

Appendix 3 – Membership of the Regenerative Medicine Expert Group

Professor Sir Michael Rawlins	Chair
Air Marshal Paul Evans	Ministry of Defence
Aisling Burnand	Association of Medical Research Charities
Alan Clamp	Human Tissue Authority
Carole Longson	National Institute for Health and Care Excellence
Charles ffrench	Constant University of Edinburgh
Chris Mason	UK BioIndustry Association / University College London
David Williams	Loughborough University
Fiona Watt	King's College London
Huw Williams	NHS Blood and Transplant
Ian Hudson	Medicines and Healthcare Products Regulatory Agency
James Palmer	NHS England
Janet Wisely	Health Research Authority
Keith Thompson	Cell Therapy Catapult
Marc Turner	Scottish National Blood Transfusion Service
Michael Hunt	ReNeuron
Nick Rijke	Multiple Sclerosis Society
Peter Thompson	Human Fertilisation and Embryology Authority
Robin Ali	University College London/Academy of Medical Sciences
Robin Buckle	Medical Research Council
Ruth McKernan	Pfizer
Stephen Field	Welsh Blood Service
Steve Bates	UK BioIndustry Association
Yvonne Wilding	Association of the British Pharmaceutical Industry

List of Abbreviations

ACI	Autologous chondrocyte implantation
B-ALL	B-cell acute lymphoblastic leukaemia
CAR	Chimeric antigen receptor
DH	Department of Health
EMA	European Medicines Agency
FDA	Food and drug administration
HSCT	Hematopoietic stem cell transplantation
HTA	Health technology appraisal
ICER	Incremental cost effectiveness ratios
NHE	Net health effect
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
QALY	Quality Adjusted Life Year
RMEG	Regenerative Medicine Expert Group
TA	Technology appraisal
TPP	Target product profile