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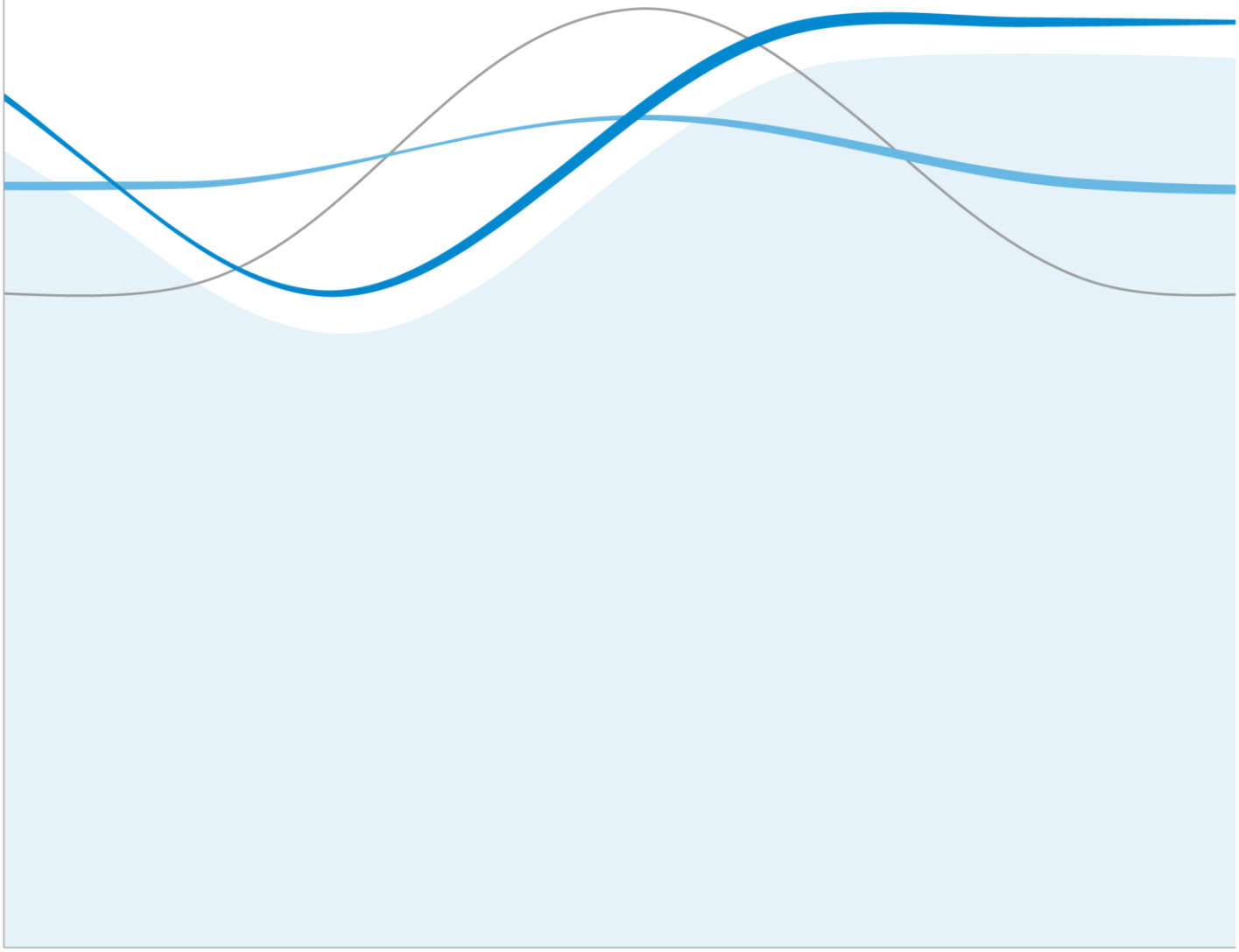
Exploring the Assessment and Appraisal of Regenerative Medicines and Cell Therapy Products: Is the NICE Approach Fit for Purpose?

February 2017

Grace Marsden and Adrian Towse



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EXECUTIVE SUMMARY

The Value of Regenerative Medicine

Regenerative medicine is an umbrella term which covers a range of medical treatments including tissue engineering, cell therapies and gene therapies. There is considerable excitement around the development of these medicines, with the expectation that that they may bring substantial clinical gains and even offer cures for previous debilitating and fatal diseases. However, valuing treatment for reimbursement purposes is challenging for two main reasons: 1) data is often insufficient for calculating robust estimates of clinical and cost-effectiveness, and 2) list prices sought by manufacturers are generally high.

The NICE Review Exercise

In March 2016, the Centre for Reviews and Dissemination and the Centre for Health Economics at the University of York, published the results of a review exercise ("the York report") which was undertaken to determine whether the existing methods and processes of the UK's National Institute for Health and Care Excellence (NICE) are appropriate for assessment of regenerative medicines. The exercise was based on a review of previous evaluations of regenerative medicines by NICE and other HTA bodies, plus a "mock technology appraisal" of a hypothetical regenerative medicine product. The stated objective of the research was to "investigate the application of existing NICE appraisal methodology to regenerative medicines, identifying challenges and areas where adaptation may be appropriate" (Hettle et al., 2016). A summary of the results and NICE's conclusions were published separately (NICE, 2016a).

The purpose of this report is to review and summarise review the exercise and to assess whether or not the resulting conclusions are appropriate.

The product chosen for the mock appraisal was CAR (chimeric antigen receptor) T-cell therapy specific to the antigen CD19, for treating relapsed or refractory B-cell acute lymphoblastic leukaemia. Incremental costs, quality adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) were calculated as per the usual NICE process, but two additional sets of calculations were also performed:

- Additional parameters: population level incremental Net Health Effect (NHE) and the consequences of decision uncertainty;
- Various payment scenarios: a lifetime leasing method; 10% discount on the acquisition cost of the intervention; payment only for patients who are in remission.

Following review of the results by an expert committee, the NICE report concludes that: (i) the existing appraisal methods and decision framework are applicable to regenerative medicines; (ii) quantification of decision uncertainty was key in decision making; (iii) where uncertainty is substantial, innovative payment mechanisms may play an important role and facilitate timely patient access; and (iv) choice of discount rate is extremely important and has a big impact on the ICER.

Our Findings on the Exercise

In our view the York and NICE exercise provided a thorough mock appraisal of CAR T cell therapy. However, it did not seek to identify the *most suitable* approach for assessing regenerative medicines, but rather to test whether regenerative medicines *could* fit into the existing pathway developed for conventional medicines. NICE concluded that they could, with the implication that this means the current methods are fit for purpose in respect of all regenerative medicines. We note that many (if not all) technologies, including those which are currently assessed via the highly specialised technologies programme, *could* be assessed within the existing technology appraisal process if necessary, but they are not required to do so. The question is, arguably, not whether or not it is possible to assess regenerative medicines by existing means, but whether or not this is the most suitable route.

Several flexibilities already exist within the current NICE process (such as differential discount rates where substantial benefits are expected long term, inclusion of non-health benefits in particular circumstances, acknowledgement of weaker evidence where it is difficult to conduct full RCTs) that will apply to many regenerative medicines. As such, we agree that many regenerative medicines will be adequately assessed within one of NICE's current programmes (the expectation is that some will be routed through the TA process and some through the HST programme, whilst others may not be seen by NICE at all). However, regenerative medicines are likely to meet problems at the extremes, such as when there is substantial decision uncertainty, or when substantial clinical benefits (or cures) are offered at very high cost. It would be helpful if NICE could issue an update to their methods in respect of issues that might be expected to arise with regenerative medicine, or a separate summary document that outlines how relevant flexibilities are expected to apply to regenerative medicines.

Uncertainty and innovative financing mechanisms

NICE have committed to exploring the quantification of decision uncertainty, which was clearly very important in the CAR T exercise. We question the relevance of the additional parameters of uncertainty around the use of NHE that were presented to the expert panel, and find that they are potentially misleading. We note that NICE did not endorse these. The York exercise was, however, very helpful in illustrating the potential impact of innovative financing mechanisms and we agree that further work is needed to explore how these could be incorporated into an appraisal process.

Further research

In addition to the points above, we note that the York team also made further suggestions on how the current technology appraisal process could be modified. These include amending the EoL criteria and criteria for allowing use of a 1.5% discount rate.

Any significant departures from the usual TA or proposed HST processes must be based on solid economic rationale if we are to ensure efficient allocation of NHS resources. This report acknowledges that many of the key issues likely to be faced by regenerative medicines are not unique to these technologies - the unique problem is that these medicines are likely to face a higher concentration of these problems. Further research will help shed light on whether or not there exist solid economic grounds for valuing regenerative medicines differently to conventional medicines.

1. INTRODUCTION

1.1. Regenerative Medicines and Cell Therapy Products

Regenerative medicine is an umbrella term which covers a range of medical treatments including tissue engineering, cell therapies and gene therapies. It is described by the House of Lords Science and Technology Committee as "[a group of] *methods to replace or regenerate human cells, tissues or organs in order to restore or establish normal function*" (Science and Technology Committee, 2013). Mason and Dunhill (2008) explain that the central focus of regenerative medicine is human cells, and suggest that there are a number of medical conditions which may potentially be treatable with these cell-based therapies, such as heart failure, insulin-dependent diabetes, spinal cord injury, Parkinson's disease and Alzheimer's disease.

There is considerable excitement around the development of regenerative medicines, with the expectation that that they may bring substantial clinical gains and offer cures for previous debilitating and fatal diseases. Karathanasis (2014) describes regenerative medicines as "an unprecedented opportunity to transform traditional pharma research and development (R&D) and revolutionize future medical practice*";* Mason and Dunhill (2008) comment that regenerative medicines have the potential to be 'disruptive technologies', transforming clinical pathways and replacing a number of existing drugs and devices (Mason and Dunhill, 2008).

However, the promise of large clinical gains is not sufficient to bring these therapies to market. Faulkner (2016) refers to "a complex and sometimes baffling range of pathways, routes, hurdles and so on" which must be overcome before regenerative medicines reach clinical practice, and Abou-El-Enein et al. (2016a), explain that even therapies that demonstrate "remarkable" clinical benefits, still may not reach patients, in part because of the need to estimate long term benefit past the time period of RCTs.

Securing reimbursement is a significant hurdle for manufacturers for two main reasons.

- Firstly, insufficient data for calculating clinical and cost-effectiveness is a common problem amongst regenerative medicines (REGenableMED, 2016). For example, two autologous chondrocyte implantation (ACI) products for cartilage defects in the knee have received marketing authorisation in the EU, but have not secured reimbursement in most European markets including the UK. NICE guidance released in 2015 stated that ACI could only be recommended in research because the evidence of clinical effectiveness was inconclusive (REGenableMED, 2016).
- Secondly, high list prices. This may reflect one or more of high R&D and manufacturing costs, the size of the treatment impact on patients relative to other available treatments, and the potential to reduce future healthcare costs. In one extreme example, Glybera, only of only two licensed gene therapies in Europe, reportedly comes with a €1.1million price tag (Ylä-Herttuala, 2015). Strimvelis, the other, is reported to have a price tag of €594,000 (Abou-El-Enein et al., 2016a). Faulkner (2016) reports the disconnect between market authorisation and reimbursement is most extreme in South Korea, where 16 regenerative medicines have been approved (to 2014), but none have secured reimbursement.

1.2. The NICE CAR T Exercise

Health technology assessment (HTA) bodies, such as the UK's National Institute for Health and Care Excellence (NICE), conduct value assessments of new technologies which are often used to inform reimbursement decisions. NICE has several different assessment programmes for different types of technologies, including the Technology Appraisal (TA) programme for medicines, Highly Specialised Technologies Programme (HST) for treatments for rare diseases, the Medical Technologies Guidance (MTG) programme for medical devices, and the Guidelines programme which makes evidence-based recommendations on a wide range of health and social care topics. The TA and HST programmes seem the most likely candidates for assessment of regenerative medicines[1], depending on the size of the population, and they could also be assessed as part of the wider clinical pathway within the clinical guidelines programme. However, until recently, no research had been done into whether NICE's current methods were appropriate for reviewing these types of technologies.

In March 2016, the Centre for Reviews and Dissemination and the Centre for Health Economics at the University of York, published the results of an exercise undertaken to determine whether NICE's existing methods and processes are appropriate for assessment of regenerative medicines (Hettle et al., 2016 or "the York report"). The exercise was undertaken in response to an inquiry into regenerative medicines by the UK House of Lords. The inquiry led to the establishment of a regenerative medicines expert group (RMEG) and subsequently the development of an action plan for the NHS. RMEG suggested that NICE commissioned a mock appraisal to assess whether changes to its methods and processes were needed.

According to NICE (2016a), the stated objectives of the analysis were:

- To test the application of NICE appraisal methodology to regenerative medicines, 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 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 and cost-effectiveness and to identify the most important evidence areas to develop before cost-effectiveness can be reasonably estimated.

The exercise was based on a review of previous evaluations of regenerative medicines by NICE and other HTA bodies plus a "mock technology appraisal" of CAR T-cell therapy for the treatment of acute lymphoblastic leukaemia ("the CAR T exercise"). The stated objective of the research was to "investigate the application of existing NICE appraisal methodology to regenerative medicines, identifying challenges and areas where adaptation may be appropriate" (Hettle et al., 2016).

At the same time, in March 2016, NICE published a report (NICE, 2016a) which included a summary of the York exercise and NICE's inferences about what the research meant for its processes and methods.

[1] Regenerative medicines can also be devices, but devices are only routed through MTG if they are expected to be cost saving or cost neutral which is unlikely to be the case for regenerative medicines. The costs of regenerative therapies are discussed in section 2.2.1.

1.3. This report

The purpose of this report is to review and summarise the CAR T exercise and to assess whether or not the resulting conclusions are appropriate. We draw heavily on the analysis undertaken by the University of York (Hettle et al., 2016) and the related NICE publication (NICE, 2016a).

This report is structured as follows:

- It begins with a summary of the key issues which could be faced by regenerative medicines throughout development, evidence generation, and HTA;
- Next, we outline the key findings and discussion points reported in the York report (Hettle et al., 2016) and the NICE report (NICE, 2016a).
- We then discuss key aspects including the choice of therapy within the exercise, the remit of the review, the departures that were taken from the usual TA process, and current flexibilities within the NICE methods which may apply to regenerative medicines. We also highlight a number of areas for further research.
- We end with a summary of our conclusions.

2. WHAT MAKES REGENERATIVE MEDICINES DIFFERENT?

2.1. Methods

2.1.1. Literature Review

We conducted a selective literature review to identify key issues likely to be faced by regenerative medicines. The review was intended to build upon our existing knowledge in this area, to provide a list of key areas which make regenerative medicines different. The review was not intended to be systematic as the main aim was to identify the key topics, rather than to identify all of the literature in this area. The purpose of the list was to provide a checklist for comparison with those which were considered within the CAR T exercise.

We chose to use a method of literature search called bidirectional citation searching (see Hinde and Spackman, 2015). Bidirectional citation searching involves starting with a small number of key relevant papers and searching the references and citations of these papers for relevant literature. Any new papers that are identified are added to the pool, and once again the citations and references of these papers are searched. Typically, the process is then repeated until no new relevant papers are identified.

We chose this approach for three reasons:

- Whilst we were interested in how these differences would ultimately affect HTA, we did not want to restrict our search to HTA-focused papers, and did not have strong preconceptions about the types of articles which would be useful to inform generation of the list;
- The nature of the literature in this area is that multiple different names for similar or overlapping therapy groups can be used;
- Bidirectional citation searching has been shown to be a powerful tool for identifying relevant papers, particularly when it is difficult for researchers to pre-specify key identifying factors of relevant literature (Hinde and Spackman, 2015).

We began with two key papers: Faulkner (2016) and Bubela et al. (2015), which were identified based on our existing knowledge. We began with the bidirectional citation searching approach outlined above and supplemented this with a search in Google with various combinations of the terms "HTA", "Health technology assessment", "gene therapy", "cell therapy", "regenerative medicine" and "tissue engineering" to collect any unpublished or grey literature.

We included studies which commented on the issues or challenges that are likely to be faced by regenerative medicines. We did not include general drug development challenges, only those which were discussed in the context of regenerative medicines, but we acknowledge that not all of the issues included here are unique to regenerative medicines. We chose to concentrate on papers that comment on and explore these issues, rather than methodological studies or individual HTA assessments of existing regenerative medicines, so as to avoid duplicating the thorough reviews which were undertaken by Hettle and colleagues in the York report.

Given that our review was not intended to be systematic, we stopped searching once relevant papers were no longer highlighting new issues for consideration. We draw mainly from six key references: Abou-El-Enein et al. (2016a); Abou-El-Enein et al. (2016b); Bubela et al. (2015); Mistry et al., (2015); Towse (2014); van Schothorst et al. (2014).

2.1.2. Use of the York report

Hettle and colleagues (2016) undertook several reviews in the York report in order to identify HTA specific methodological issues relevant to regenerative medicines. They looked at:

- EMA, NICE and FDA assessments of regenerative medicines licensed in the EU;
- the use of surrogate endpoints in clinical research, in particular for evidence as to how well surrogates predicted meaningful clinical benefits for patients;
- the extent of and direction of biases likely to affect results of non-randomised studies (including single arm trials) as compared to randomised studies.

We reviewed these searches with a view to including any relevant key issues for us to add to our list. No additional topics were identified, but each of the reviews did provide useful information enabling us to explore some of the issues further, in particular looking at the possible impacts of the various types of bias that may arise during the evidence generation process. The York report is referenced in the following results section where it was used to provide such information.

2.2. Results

2.2.1. Key issues facing regenerative medicines

The list of potential issues can be separated into several key areas: clinical evidence generation (on efficacy, effectiveness); safety; assessing and paying for value; handling uncertainty; manufacturing; and the organisation of service delivery within the health system. Note that many of the reasons (and indeed the areas) overlap. Note also that not all of these issues will be applicable to all regenerative medicines.

1: Clinical evidence generation

Standard evidence drug approval pathways (i.e. conducting multiple phases of RCTs) may not be suitable for the development of regenerative medicines due to the characteristics of these therapies (Bubela et al., 2015).

- The York report notes that some regulators and payers do recognise that conducting RCTs can problematic within some indications (Hettle et al., 2016). They provide the example of when the population is small: **small populations** mean that recruitment to an adequately sized RCT can be problematic, expensive, take a very long time and pose statistical challenges. These difficulties have been recognised within the HST programme. Regenerative medicines will not necessarily always have small population sizes, but this is likely to be a concern for many of them.
- It can be difficult to **identify the appropriate comparator** for the regenerative therapy to be assessed against, particularly where the regenerative therapy leads to marked changes in clinical practice or where there is no existing therapy. A report published by the European Commission (van Schothorst et al., 2014) explains that where no standard or comparable treatment is available, there may not be any clear clinical pathway or established measures of clinical outcomes. In such circumstances, manufacturers must work with physicians to develop appropriate outcome measures. This requires additional time and resources.
- In such cases where no alternative treatments exist, and when the treatment is for a life-threatening condition, it may be deemed **unethical to withhold experimental treatment** from participants within a trial due to a lack of clinical equipoise. Evidence must still be generated for these treatments, for example through single-arm trials. This type of evidence, however, gives rise to further problems, as we discuss below.
- Key trials may necessarily depend on **surrogate outcomes** requiring HTA bodies and payers to extrapolate to clinical endpoints. The York review of literature exploring the use of surrogate endpoints found that, where a comparison can be made, trials using surrogates tend to report larger estimates of treatment effect (28%-48%) than those reporting clinical endpoints. This raises questions over the validity of any surrogates explored in a trial.
- The **mode of delivery** for regenerative medicines can be more complicated than for conventional medicines. Abou-El-Enein et al. (2016a) provide the examples of ChondroCelect and MACI which are cellular products that are administered via two-stage surgical procedures; one for tissue harvest and another for implanting resulting cell products. Invasive methods of administration such as these may require "sham" operations in order to conduct blinded RCTs. Such sham operations can be costly and unethical and may ultimately prevent placebo-controlled trial designs (van Schothorst et al., 2014).
- **Single arm trials** may sometimes be necessary due to the aforementioned difficulties in conducting RCTs. In such cases it can be difficult to identify a comparator dataset. The York review of literature on the use of single arm trials found that, unless good quality historical control data is available, the natural history of the disease is well known, and the patient population is homogenous, single arm trials are unlikely to produce reliable estimates of benefit.

- Given the difficulties conducting RCTs, **observational level evidence** may sometimes be utilised for regenerative medicines. Observational level evidence is generally less well received by regulators and HTA bodies as it is at greater risk of bias. The York report notes evidence from comparisons of RCTs and non-randomised studies of the same interventions that indicated that study design was a factor impacting on the reliability of observational studies. Retrospective studies and historical control studies are more likely to result in biased estimates of effect. Prospective studies were more reliable.
- It has been suggested that the efficacy of the product is likely to vary depending on the **delivery protocol** and the **skill of the surgical team** (Abou-El-Enein et al., 2016a). Hettle and colleagues comment in the York report that this could generate high variation in response across individuals and centres, leading to implications for the generalisability of efficacy and safety estimates, particularly those generated by small, single-centre, single-arm trials. Where skill of the surgical team is a relevant concern, there could also a 'learning effect' over time which serves to improve the effectiveness of the treatment[2].
- Generalisability of evidence may also be an issue across **different iterations of the regenerative medicine product**. These types of therapies are constantly being developed, thus posing problems for long term evaluations. Indeed, returning to the example of ACI technology being assessed by NICE, the evidence review group report highlights the "general problem when long-term results are needed but the technology continues to evolve". By the time sufficiently long-term trials results are available, the therapy may have already been superseded (Mistry et al., 2015; Hettle et al., 2016).

2: Safety Concerns

Regenerative medicines come with their own set of **safety concerns**; they can be tumorigenic and can give rise to proliferation in tissues which have not been intentionally targeted (van Schothorst et al., 2014). They can also stimulate immune reactions, meaning immunotherapy is required, thereby adding to overall risks (Abou-El-Enein et al., 2016a). The issues around potentially invasive routes of administration can also give risk to further safety concerns.

3: Assessing and Paying for Value

The challenges to getting good evidence complicate the assessment of long term value, and high prices can also generate affordability challenges. More specifically:

- Regenerative medicines are often associated with **high prices per patient**, meaning it can be difficult to reach standard cost-effectiveness thresholds set out for conventional medicines. These high prices may be driven by high costs due to:
    - higher R&D costs due to problems with translating basic science into a treatment, and clinical evidence generation (for example small population

[2] Whilst NICE does sometimes note the existence of a possible learning curve effect within its guidance (typically device related guidance), this is not generally accounted for quantitatively within modelling estimates. The York report notes the potential importance of these effects but does not include them in the modelling exercise.

sizes mean that trial recruitment is likely to take longer, thereby increasing costs[3]);

- the personalised nature of regenerative medicines, meaning that manufacturing costs are likely to be higher; products cannot necessarily be prepared, tested, and manufactured in bulk as they would be with small molecule drugs. Rather, specialist manufacturing facilities may be required. Abou-El-Enein et al. (2016b) comment that for many cellular products, the major cost driver is the duration of the manufacturing process, as there is a linear increase in these costs;
- costs of clinical delivery: changes in infrastructure and the current service delivery model may be necessary that increase the costs of clinical delivery. The existing NICE appraisal for ACI (NICE 2016b) comments on the lack of appropriate cost values for other elements of the procedure (i.e. those which would be incurred by the NHS in addition to the cost of the therapy itself) which was challenging due to limited experience of the product in the clinical setting. We expect that the introduction of new elements of clinical care is likely to increase costs as compared to current treatments;
- small market sizes, as noted in the previous sections, meaning that manufacturers have fewer potential patients from whom they are able to recover R&D costs, and thus may seek to set higher per-patient prices.

- Regenerative medicines are expected to offer **greater clinical gains** than conventional therapies: Bubela et al. (2015) comment that "the promise of regenerative medicine is to break out of the marginal value mould of traditional pharmaceuticals with curative therapies for indications with limited treatment options". This has three implications:

  - Long lasting curative effects are likely to reduce ongoing costs such as patient support and managing chronic comorbidities, thereby offsetting high upfront costs and may help to justify the high prices of these therapies (Abou-El-Enein et al., 2016b).
  - Curative therapies may be valued more highly by society than treatments that offer marginal gains, and such weighting is not included in typical HTA value assessments.[4]
  - There is likely to be an inherent disconnect between the timing of payment for potentially one-time curative medicines and the cost-offsets/health

[3] Although it has been argued that orphan drugs have lower clinical development costs, because small patient numbers mean smaller trials and lower expenditure. Trial costs depend on: costs-per-patient; numbers of patients; and time, which generates an opportunity cost.

[4] When the UK Department of Health proposed "Value-based Pricing" it included a proposal for treatments offering a high QALY value to get higher prices than would be justified by the health gain alone. This proposal was dropped when survey work found that whilst there was evidence that the public gave a weighting to tackling more severe diseases, there was consistently a diminishing marginal social value from QALY gains (Rowan et al. 2016). It could be argued that a curative treatment reduces severity as the effects of treatment progress, such that the value of the QALYs gained falls. Alternatively, there may be benefits to disease eradication beyond the health gain. This issue has been actively explored in the case of infectious diseases such as malaria (Lui et al. 2013) and HCV.

benefits that may result, but that may only be realised over decades after the therapy is administered. The differential timing of benefits and costs is considered within NICE's current appraisal process via the use of discount rates. The discount rate quantitatively captures time preference, reflecting the concept that we prefer health benefits (or any other type of benefit) to be accrued sooner rather than later, but costs to be incurred in the future. The choice of discount rate (reflecting the strength of time preference) may, however, be very important in assessing some regenerative medicines. We discuss the implications of timing issues for affordability below.

- Regenerative medicines may be associated with **high levels of irrecoverable costs** due to the high upfront costs of equipment and procedures, as well as investment in changes in infrastructure and clinical pathways. These costs may not be recoverable should implementation of the technology need to be reversed due to new data (for example new safety concerns) or improved treatments.

- Regenerative medicines may give rise to **affordability issues** in two different ways:

    - High prices, even with small patient numbers, can put pressure on health system budgets.

    - The inherent disconnect we referred to above, between the timing of payment for potentially one-time curative medicines and the cost-offsets/health benefits that may result, can mean that products that may be good value for money by reference to current cost-effectiveness thresholds still put a strain on a payer's budget. This can arise from the fact that all of the health gains are paid for up front, rather than on a typical per month basis over many years with a chronic therapy. Healthcare systems are generally not configured to pay for new products in a manner other than price per unit of input (be it vial, treatment, or procedure). Possible solutions that use financing mechanisms to realign costs and benefits are discussed by Tapestry, 2016, and the York Report looks at a leasing option. We return to this topic later.

4: Uncertainty

Uncertainty for healthcare decision makers about the impact of regenerative medicine arises primarily because of the limited evidence base at launch (as a result of small populations, surrogate outcomes, single arm studies, and lack of resource estimates for the existing clinical pathway) and the need to extrapolate long term benefits and address any potential safety concerns.

Uncertainty matters in decision making, as greater uncertainty increases the probability of making a wrong decision. In the case of HTA decision making looking at cost-effectiveness, uncertainty should be dealt with in a two part assessment. Firstly, looking at whether the best estimate of the ICER is within the relevant cost-effectiveness threshold or other value hurdle, and secondly, using a value of information framework (looking at the costs and benefits of collecting more evidence) to assess whether it would make economic sense to collect additional evidence to reduce the uncertainty, and

whether this should be done whilst the technology is being used – a form of coverage with evidence development (CED)[5] – or before any adoption decision? The question arises as to what more evidence could be collected pre-launch? One could, of course, run longer trials, but if they continue to show evidence that the effect is positive, more patients who could benefit do not get access. The returns to R&D investment also fall, assuming no change in price, because of the delays in getting any revenues, reducing the likelihood of future investment in similar disease areas[6].

In this context two other factors might come in to play:

- Firstly, there may be sunk costs or irreversibilities associated with adopting the technology, which need to factored into any additional evidence (including CED) decision making.
- Secondly, some sort of pay-for-performance arrangement may be an alternative may of addressing the uncertainty from the payer's point of view.

5. Manufacturing and the Organisation of Service Delivery

Some regenerative medicines – particularly *ex vivo* autologous therapies that involve extraction and manipulation of patients' own cells – are highly complex and involve different procedures separated over time, care settings, and even geography, which may challenge healthcare systems that are set up around more conventional therapies. In particular:

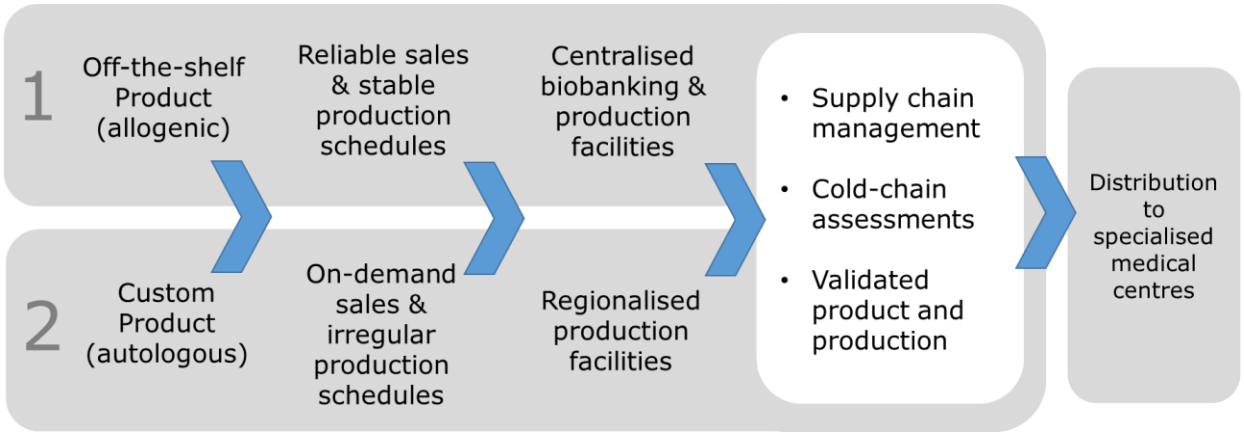
- As mentioned previously, the personalised nature of regenerative medicines means that products **cannot necessarily be manufactured in bulk** unlike both small and large molecule drugs. Therefore, even if the manufacturer does manage to secure reimbursement, there may still be service delivery hurdles to be overcome.
- Cell therapies can have **short shelf lives** and are sensitive to their surrounding conditions. Abou-El-Enein et al. (2016a) provide the example of Holoclar manufacturing which requires that patient biopsies must be received by the manufacturer less than 24 hours after they are taken from the patient. Once developed, the product only lasts for 36 hours in controlled conditions. Such restrictions are costly and logistically challenging. Figure 1 below contrasts the supply chain for regenerative medicines and conventional therapies.
- Concerns have also been raised that a **lack of clarity around manufacturing and quality standards** for regenerative medicines may result in inefficient product development and act as a barrier for development. This is likely to be particularly problematic in rare diseases where no precedents exist (van Schothorst et al., 2014). There is a trade-off between allowing flexibility in the

[5] The case for CED usually arises when the best estimate of the ICER is that it is cost-effective but there is substantial uncertainty. A discussion of the potential merits (or otherwise) of CED is outside of the scope of this report. See, for example, Walker et al. (2012) for a discussion. We can note that NICE already has mechanisms to introduce CED via Patient Access Schemes and Managed Access Schemes. In addition the arrangements that came into place from 1st April 2016 in relation to cancer drugs create a new mechanism for CED.

[6] Of course, the innovator might find that the additional evidence justifies a higher price. However, unless this is an unexpected improvement in the mean outcome, the value of reducing uncertainty – in terms of getting a higher price for less uncertainty - should have been factored into the innovator's original choice of clinical trial size and length.

manufacturing process to account for the patient-specific nature of the products and the need to establish good manufacturing practice through standardised practices (Abou-El-Enein et al., 2016b).

Figure 1: Supply chain for regenerative medicines and conventional therapies



Source: Abou-El-Enein et al., 2016a.

- The specialised nature of regenerative medicines may lead many payers to insist that these treatments are provided only in a few centres of excellence. In the case of some treatments, patient numbers and required investments in facilities and skills may be such that there are only a few centres in Europe.

2.2.2. Are these issues unique to regenerative medicine?

Many issues face regenerative medicines from the early stages of development through to reimbursement, manufacture and delivery in the health system. However, it is unclear how many of these are specific to regenerative medicines, and how many also apply to other therapy areas. For example: all orphan designation medicines are at risk of problems associated with small disease populations on both RCT design and on price per patient; the effectiveness of many surgical procedures is likely to be effected by delivery protocol and levels of provider skill; medical devices face the problem of short development cycles and frequent product iteration; curative therapies which are not regenerative medicines offer high benefits at high costs.

In a presentation at ISPOR 17th Annual European Congress, Towse (2014) argued that several of the challenges for "one-off" curative regenerative medicines are about generating evidence about cost-effectiveness, and that these are the same challenges as those faced by more conventional disease modifying therapies for chronic diseases, namely:

- Short term trials often rely on surrogate markers;
- Outcomes may not be sustained over time; and
- Safety problems can emerge.

We have discussed earlier the potential for CED with post-launch data collection. Two chronic disease analogies are:

(i) the initial surveillance requirements that were necessary comparing new biological agents for rheumatoid arthritis (RA) with the then current Disease-modifying anti-rheumatic drugs (DMARDs) via the British Society for

Rheumatology Biologics Register (BSRBR-RA) which included six month safety assessments and administration of a disease specific health status instrument (DAS-28) (Watson et al., 2005); and

(ii) the British Association of Dermatologists Biologic Interventions Register (BADBIR) established to look at the long-term safety of biologic treatments for psoriasis when they entered the UK market, with six month reviews of adverse events, and of health status via the Dermatology Life Quality Index (DLQI) as well as the EQ-5D (Burden et al., 2012).

Towse (2014) went on to argue that the real difference between conventional disease modifying therapies for chronic diseases and "one-off" curative regenerative medicines is likely to be budget impact (affordability). We can note in this context that:

- the current (interim) NICE guidance for the HST programme includes a requirement to "take into account the total budget for specialised services" (NICE, 2013b);
- the consultation issued by NICE and NHS England (NHSE) (2016) proposes that where the budget impact is greater than £20m or, in the case of an HST, the cost per quality adjusted life years (QALY) was above £100,000, new processes involving the payer, NHSE, would be used.

Hettle and colleagues comment in the York report that:

- None of the issues that they identified (all of which are included in the list above) are *unique* to regenerative medicines, but;
- Many of the challenges are likely to be *more common* amongst regenerative medicines and cell therapies.
- Many regenerative medicines and cell therapies will be considered as both a biologic and a device, and therefore developers may be required to address the regulatory and reimbursement challenges faced by both pharmaceuticals and devices.

While no single issue on its own may be problematic, the totality of these considerations may create challenges for stakeholders and policy makers, by impeding evidence generation, valuation, reimbursement and ultimately adoption and delivery of regenerative medicines.

3. THE CAR T EXERCISE

3.1. The York report

3.1.1. The Decision Problem, Scenarios and Results

The main purpose of the CAR T exercise was to conduct an exemplar NICE appraisal of a hypothetical regenerative medicine product. The hypothetical product chosen was CAR (chimeric antigen receptor) T-cell therapy specific to the antigen CD19, for treating relapsed or refractory B-cell acute lymphoblastic leukaemia (B-ALL). Depending on the specific type of CAR T therapy, these treatments may offer patients either (i) a 'bridge' to a stem cell transplant or (ii) a possible cure (without the need for transplantation). However, serious adverse effects (such as cytokine release syndrome and B-cell aplasia) are also possible.

This choice of therapy for this mock appraisal was made for practical reasons, as some relatively mature data sets were available whilst none of the existing CAR T-cell products are licensed. The population, comparator and outcomes chosen are outlined in Table 1.

Table 1: CAR T decision problem

Population	Patients with B-cell acute lymphoblastic leukaemia (B-ALL) who have relapsed (with no further planned curative chemotherapy or haematopoietic stem cell transplant (HSCT)) or who are refractory (i.e. non-responsive or resistant) to standard chemotherapy.
Intervention	CD19 CAR T-cell therapies
Comparator	Best supportive care (e.g. salvage or rescue chemotherapy given after non responsiveness to standard therapy)
Outcomes	• Response criteria: complete response/remission (CR), partial response/remission (PR), and negative minimal residual disease (MRD); • Overall survival (OS); • Progression and/or event-free survival; • Persistence of CAR T-cells to support therapeutic response; • Health-related quality of life; • Rates of HSCT; • Adverse events: Cytokine release syndrome (CRS), B-cell aplasia, febrile neutropenia, or other adverse neurologic effects.
Subgroups	Possible sources of heterogeneity in response, such as relapsed/refractory status, previous HSCT, CAR design, dose, conditioning chemotherapy, tumour burden at the time of therapy, or age of the patients.

Source: Summary of data available in the York Report

Two target product profiles (TPPs) were developed:

- CAR T-cell therapy used as a bridge to stem cell transplant (i.e. the goal of treatment is to induce short-term remission of disease and create opportunities for haematopoietic stem cell transplantation (HSCT);
- CAR T-cell therapy used with curative intent.

For each TPP, three datasets were developed: minimum (representing the minimum level of evidence which would likely be available for a treatment to receive regulatory approval), intermediate, and mature (see Table 2).

Table 2: Summary of the sample size and maturity of evidence assumed in the 3 evidence sets

	Minimum	**Intermediate**	**Mature**
Sample size	60-80	60-80	120-140
Study follow up	10 months (median)	60 months (maximum)	60 months (maximum)

Source: The numbers are taken from Table 8 of the York Report

Overall, therefore there were six data sets – three for each of the two TPPs. A decision model was then developed for each TPP, and incremental costs, QALYs and incremental cost-effectiveness ratios (ICERs) were calculated. A summary is provided in Table 3.[7]

Table 3: Summary of cost effectiveness results from the York report

Dataset	ICER	Decision about whether or not treatment would be recommended	Probability cost effective
TPP1: bridge to stem cell transplant			
Minimum	£55,090	No	26.1%
Intermediate	£55,090	No	26.1%
Mature	£53,462	No (assumed)	28.1%
TPP2: curative intent			
Minimum	£50,906	No	50.7%
Intermediate	£43,344	Borderline	85.9%
Mature	£43,252	Borderline/Yes	91.5%

Abbreviations: ICER = Incremental cost effectiveness ratio; TPP = target product profile.
Source: Summary of information from the York and NICE reports.

We comment on these results in section 4.4.

In addition to this conventional approach to preparing an evidence assessment, the York team did two further sets of calculations.

1. They calculated two additional parameters. The additional parameters were: 1) population level incremental Net Health Effects (NHE), which they define as the "difference between any health gained with the intervention and health foregone elsewhere in the health system" at the relevant cost-effectiveness threshold (thus if a technology is only just cost-effective the NHE is close to zero) and 2) the consequences of decision uncertainty calculated as the potential magnitude of NHEs that could be gained if the uncertainty surrounding potential decisions could be resolved (expressed in terms of costs and QALYs).
2. They calculated various payment scenarios in addition to the one-off purchase of the product. These were:
    a. A lifetime leasing method where a monthly fee is paid for the duration of the benefits (until death);
    b. A 10% discount on the acquisition cost of the intervention;
    c. An outcomes-based payment model, where payment is made only for patients who are in remission (this led to approximately a 35% reduction

[7] See pages 99-176 of the York report for a detailed description of the models and their inputs.

in cost per patient in the case of TPP1 and a 10% reduction in cost per patient in the case of TPP2)[8].

The results of these additional calculations for one of the six data sets - the curative intent TPP using the minimum dataset - are provided in Table 4 for illustrative purposes. These additional parameters and payment scenarios are not normally calculated as part of the NICE TA process.

Table 4: Results from TPP2: Curative Intent (minimum evidence set)

Scenario	**ICER**	**Incremental NHE** QALY (£)	**Probability cost-effective**	**Consequences of decision uncertainty** QALY (£)	**Decision on whether or not treatment would be recommended**
Base case	£50,906	-56 (-£2.9m)	50.7%	304.6 (£15.2m)	No
Lifetime leasing method	£50,618	-38 (-£1.9m)	49.2%	65.6 (£3.2m)	No
Discount of 10% on base case acquisition cost	£45,131	306 (£15.3m)	64.2%	209.1 (£10.5m)	Borderline/ No
Payment for patients with remission only	£45,708	267 (£13.3m)	63.9%	236.1 (£11.8m)	Borderline/ No
Discount of 10% on base case price with lifetime leasing	£45,502	275 (£13.7m)	87.2%	27.2 (£1.3m)	Assumed Borderline/ Yes

Abbreviations: ICER = Incremental cost effectiveness ratio; NHE = het health effect
Source: Summary of information from the York and NICE reports, taken from Table 3 of the NICE Report.

3.1.2. Discussion of the Results by the Expert Panel

A summary of the results were presented to a panel made up of clinical experts and current and past NICE Appraisal Committee members.

The therapy was assessed using the TA approach and not the HST programme approach. The panel agreed that NICE's end of life (EoL) criteria[9] were met for this therapy, which

[8] Note that the outcomes-based payment method appears to produce a lower ICER than the lifetime leasing method. This may reflect the different cut-off points – end of remission and death respectively.

[9] The usual cost-effectiveness threshold for decision making in NICE TAs is £20,000-£30,000, with a base of £20,000 rising up to £30,000 if additional factors merit this in the view of the Appraisal Committee. However, in specific circumstances, when the "end of life criteria" are met, the

means that the relevant cost-effectiveness threshold was £50,000. Whilst significant benefits may be sustained over long periods of time, the panel did not conclude that the lower 1.5% discounting rate[10] could be applied. The York report states that "While it was noted that the existing criteria had been developed in response to a similar decision context, (it)...had only been applied in 1 previous appraisal. ...The use of stepped-discounting recommended by the Treasury was discussed by the panel but considered to be more relevant for...inter-generational impacts (e.g. immunisation) as opposed to longer-terms inter-generational effects."[11] The impact of both the discount rate and EoL criteria are discussed in section 4.2.

The modelling was constructed to create scenarios with ICERs in the range of £30,000-£50,000 per QALY to stimulate discussion of relevant issues by the panel. The key difference between the datasets was in the level of uncertainty around the mean estimate with degree of confidence in the mean estimate increasing with maturity of the dataset. Typically those based on the minimum evidence set also had the highest ICERs. This, however, reflected the modelling approach rather than any expectation that a more mature dataset would necessarily lead to a lower ICER.[12] The use of lifetime leasing payment methods or payment only for patients in remission reduced the ICER to more acceptable levels in the view of the panel. Whenever the ICER was above the acceptable cost-effectiveness threshold, the panel concluded that the treatments could not be recommended; whenever the ICER was marginally below the threshold but uncertainty was high, the panel indicated a "borderline" or "no" recommendation. For full details see Chapter 9 of the York report. As we can see from the results shown in Tables 3 and 4 above, very few scenarios resulted in a "yes" decision.

Key points raised by the panel included:

- Uncertainty:
    - The level of uncertainty in the evidence base was a cause of significant concern, specifically that due to the single-arm trials and extrapolation from short term data (particularly within the minimum dataset) to long term benefits. Exploration of this uncertainty was key to decision making, and the panel felt that guidance should be in place for manufacturers on how to account for uncertainty.
    - Sources of potential bias and uncertainty will be important considerations within future appraisals; manufacturers should explain clearly how these have been addressed within their submission.
    - The level of decision uncertainty seen in this mock appraisal may be greater than that which anticipated in NICE's current methods guide.

acceptable threshold is raised to £50,000. The criteria are: 1) the treatment is indicated for patients with life expectancy less than 2 years; 2) treatment is likely to extend life by at least 3 months.

[10] Current NICE methodology dictates the use of a 3.5% discount rate in the base case. Where a technology restores severely ill people to full or near full health, and these benefits can be expected to be sustained over a long period of time, a discount rate of 1.5% can be applied if the introduction of the technology would not commit the NHS to significant irrecoverable costs.

[11] The NICE Report notes that "1.5% discounting reduced the ICER relative to the base case by 30%" (para 40, page 11)

[12] The impact of the modelling approach on survival across the datasets is discussed on pages 172 and 173 of the York Report.

  - There were important differences in the scale of the consequences of decision uncertainty across the different scenarios. Specifically, the consequences were much greater in the curative intent TPP.
  - The panel found the use of population NHE as an exploratory approach to quantifying decision uncertainty "provided important information which could help inform their deliberations for decision making" but they '"expressed difficulty in determining how to interpret the numbers presented without a formal reference point to establish whether the consequences were sufficiently high to impact on their decisions and /or potential research recommendations."
  - There may be issues around irrecoverable costs incurred by the NHS, and that a clear 'exit strategy' would be important where uncertainty was high.
- EoL criteria:
  - Whilst the EoL criteria did apply to this treatment, these criteria were not designed with curative therapies in mind. They raised concerns that the criteria were designed for situations in which treatment for people with short life expectancy provided some extension, but life expectancy remained short. It was therefore suggested that the EoL QALY weighting may need to be revised for this type of treatment. We discuss this further in section 4.2.
- Pricing models:
  - The panel noted that "the different pricing schemes had important impacts both in terms of the ICER but also in terms of the allocation of any risk between the NHS and manufacturers." The lifetime leasing model was considered to be an important option, but the panel did note that this "warranted further exploration by NICE and manufacturers" in terms of logistics, costs and feasibility.

3.1.3. Conclusions

Based on their literature reviews and this mock appraisal, Hettle and colleagues (2016) conclude that "Our findings show that the conventional assessments requested within the current TA process may not be sufficient" (Hettle et al., 2016). They argue that ICERs and the probability that a technology is cost-effective do not provide all of the relevant information for the committee and modifications to the NICE Methods Guide could be useful. For example, they suggest that presentation of the population NHE, and presenting the scale of decision uncertainty using NHE, may be helpful additions; issues of irrecoverable costs may need to be formally considered where upfront costs are expected to be high; the existence and possible impact of learning curves (although not explored in this analysis) may also be an important issue for clinical and cost-effectiveness assessments.

3.2. The NICE report

The NICE report provides a summary of the York exercise, focusing mainly on the mock appraisal part of the review. The assumptions about price and about QALY gains (from the minimum data set) are set out in Table 5 below.

Table 5: Benefits and Costs of the 2 TPPs

	TPP1: Bridge to stem cell transplant	TPP2: Curative intent
Assumed individual patient level incremental QALY gain	7.46	10.07
Assumed price (acquisition cost)	£356,100	£528,660

Source: Table 1 of the NICE Report.

It notes that the significant increase in patient benefit is beyond that which would be expected for a usual therapy, but that estimates of clinical effectiveness are subject to great uncertainty. The report also comments on the resulting high levels of decision uncertainty, acknowledging that the panel found the additional parameters developed by the York team (including population NHE as a measure of decision uncertainty) helpful. It notes that these parameters are not routinely used within the TA process. It also notes that "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".

The report also reported on the Expert Panel's consideration of the case for using the 1.5% discount rate. It stated that "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."[13]

The key findings of the report (NICE, 2016a) include the following:

- "It is clear...that the methodology and decision framework of NICE Technology Appraisals is fundamentally applicable to regenerative medicines and cell therapies".
- Where there is a combination of great uncertainty while the evidence is immature but potentially very substantial patient benefits, "innovative payment methods, such as the lifetime leasing, may have a key role to play in managing and sharing the financial risk" but where the evidence base was more mature "conventional one-off payments for products may be sustainable".
- The discounting rate applied to costs and benefits was found to have a very significant impact on analyses of these types of technologies.

The recommendations are:

- "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."

[13] The rationale given for the Expert Panel rejecting the use of the 1.5% discount rate in the NICE Report appears to be different to that given in the York Report.

- NICE further develops "the ways in which uncertainty can be quantified and presented to decision makers taking account of the framework developed by the York team."
- NICE works with others to "develop practical payment methods for managing and sharing financial risk, such as lifetime leasing."
- "NICE takes account of this study when reviewing the criteria for when the 1.5% discounting rate should be applied."

The report did not comment on the other suggestions made within the York report, such as explicit consideration of irrecoverable costs or learning curves for complex delivery protocols.

4. DISCUSSION

4.1. Choice of technology: CAR T-cell therapy

It is important to recognise that the area of regenerative medicine comprises a whole range of technologies, not all of which will face the same set of issues outlined in section 2.2. This in mind, choice of technology for this exercise was critical, as the exercise was undertaken to assess whether the process was appropriate for regenerative medicines generally, not for CAR T-cell therapy in particular. It is recognised that a therapy representative of all regenerative medicines may not exist, and that the choice taken by the York team was necessarily largely driven by practical considerations, in particular the ability to generate a plausible evidence base for modelling cost-effectiveness.

We examine how many of the difficulties outlined in section 2.2 of this report were relevant to this exercise. The relevant difficulties for CAR T therapy appear to be:

Clinical Evidence Generation and Safety Concerns:

- Large scale RCTs are not available for CAR T-cell therapy - only a small number of single arm-studies were available;
- The population is small;
- The available clinical data for the intervention is reliant upon surrogate outcomes;
- The data for the comparator is reliant on observational studies;
- The intervention has potentially serious safety concerns (side effects);

Because of the choice of CAR T, there was no analysis within the report of other potential issues which may arise in other regenerative medicines, such as: whether it was difficult to identify the comparator due to current unmet medical need meaning that little was understood about how patients were typically managed; variability due to the skill of the surgical team and delivery protocol; the iterative nature of the therapy leading to concerns with the ability to collect clinical evidence that is up to date; any ethical issues around withholding treatment in RCTs in order to create a control group.

Assessing and Paying for Value

All of the issues that we identified in section 2.2 around assessing value apply to CAR T-cell therapy:

- The therapy was assumed to come at a fairly high cost (although note that the cost was estimated specifically for this exercise and was not intended to reflect the market price);

- The therapy may offer a cure, and at a minimum is expected to offer substantial clinical gains, greater than is expected from conventional medicines;
- The therapy may be associated with high up front irrecoverable costs.

We note, however, that many regenerative therapies may offer even greater clinical benefits and come at a greater cost to the health service than the CAR T example.

Uncertainty

The choice of CAR T and its use in the York exercise led to a substantive discussion on aspects of uncertainty. Given the modelling was intended to produce ICERs around the levels of acceptability, this led to substantial decision uncertainty. The high levels of uncertainty resulting from the limited clinical data was acknowledged and discussed by the panel. The issue of irreversibilities was raised by the York Report. Alternative payment designs were explored which impacted on both the ICER and the degree of uncertainty.

Manufacturing and the Organisation of Service Delivery

Issues related to manufacturing and distribution were not explored within the CAR T study, but would be likely to contribute to the incremental cost of the technology and also concerns around irrecoverable costs.

Overall it seems that many, but not all, of the key issues for regenerative medicines were applicable for the CAR T-cell therapy. Of note, the CAR T therapy was deemed to satisfy EoL criteria, meaning that the relevant cost-effectiveness threshold for decision making was raised to £50,000. This may not be representative of many regenerative medicines, and meant that the expert panel did not thoroughly discuss the impact of further decision criteria as specified in the NICE methods guide (NICE, 2013a) such as the innovative nature of the technology, and whether all important health and non-health benefits have been captured in the context of regenerative medicines. Many regenerative medicines have the potential to be innovative products with wide reaching benefits, such as reduction in the need for care by family members and benefits of patients and carers returning to work. These additional factors could have a substantial impact on decision making for regenerative medicines, but were not explored within this analysis, as they were judged to not apply to CAR T-cell therapy in the context of the EoL adjustments.

It would therefore be interesting to explore issues that did not apply to CAR T-cell therapy but might reasonably be expected to apply to some other regenerative medicines. Specifically, the issues faced by a product that is for an ultra-rare disease (i.e. it would be assessed through the HST route), does not have an existing comparator in the NHS (severe unmet need), and is iterative in nature. This would allow exploration of some issues that were not able to be addressed within the CAR T exercise.

4.2. Application of EoL criteria and discount rate

As mentioned previously, the expert panel determined that the EoL criteria did apply to the CAR T technology. We consider that whilst, strictly speaking, this therapy may meet NICE's criteria for EoL treatments, classifying a curative therapy as an end of life treatment is a contradiction: once cured, the patient is no longer at the end of life[14].

[14] In the case of CAR T therapy, we do not consider that this is limited to the curative intent TPP, as the bridge to HSCT TPP could also lead to substantial increases in the length of life.

Assuming that the economic rationale behind the EoL criteria is that people are willing to trade quality and length of life differently at the end of life, it does not seem appropriate to apply the higher EoL cost-effectiveness threshold to the full set of health benefits that accrue from a curative therapy, as these are not all accrued at the end of life. This was also discussed by the expert panel during the mock appraisal – they commented that the existing criteria might need to be reconsidered more generally for therapies with curative potential (Hettle et al., 2016)[15].

However, if the higher threshold is not applied to curative therapies that are delivered in this situation (specifically when the patient has less than two years to live if therapy is not given), a case could arise in which a therapy would *only* be cost-effective if it did not cure the patient (if they were cured the £20-30,000 per QALY threshold would apply; but if they were not cured the £50,000 per QALY threshold would apply). We suggest that to mitigate this problem, the higher threshold could be applied over the first few years following curative treatment (practically speaking this could be done by giving the QALYs accrued within this period a higher weighting), with the normal threshold being used beyond this period. Work would need to be undertaken to determine the appropriate length of time over which the additional weighting should be applied.

Moving on to discuss the discount rate, NICE allow for a lower discount rate of 1.5% (the standard is 3.5%) where a technology restores severely ill people to full or near full health and these benefits can be expected to be sustained over a long period of time. This fits well with the concept of cures, and indeed the York report finds that the use of the lower discount rate would reduce the ICER for CAR T cell therapy by 30%. There is a third criterion, however, that the technology must not be expected to commit the NHS to significant irrecoverable costs. NICE reported that this third criterion is the reason that the expert panel did not allow the assessment of CAR T cell therapy to use the lower discount rate (no firm conclusion was reached). The expert panel also noted the lack of precedent for the use of the lower discount rate (it has only been used in one TA (reported by Hettle et al., 2016)) and suggested that its application could be the cause of debate within future appraisals.

This third hurdle is likely to be a barrier for many regenerative medicines, yet there does not appear to be any economic rationale for the link between discount rate and irrecoverable costs. It seems that, rather than being based on grounds of efficiency, this criterion is included to limit the number of technologies for which the lower discount rate can be used. It appears therefore to be rather arbitrary. If NICE truly believe that the 1.5% discount is appropriate for a technology that restores severely ill people to full or near full health and that provides sustained benefits over a long period of time, on grounds of efficiency, this should not be restricted to technologies that will not incur significant irrecoverable costs. A summary of the literature around different discount rates is provided by Hettle et al. (2016).

[15] The report stated that "… the panel also noted that the existing criteria might need to be reconsidered more generally for therapies with curative potential. It was argued by one panel member that the EoL criteria were developed to cover scenarios where people with conditions such as cancer with a short life expectancy, were given some extension, but whose life expectancy was still short. It was suggested that different QALY weights might need to be considered over a longer period of projected survival benefits for therapies which have curative potential."

4.3. Remit of the CAR T exercise

The initial referral from the RMEG subgroup was for "an exploratory study of the appraisal of example regenerative medicine products [to] 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" (NICE, 2016a). In order to do this, NICE and the York team have tested whether or not regenerative medicines can fit into the usual TA process. The NICE report then concludes that the methods are appropriate. The difficulty is that no other methods or alternatives were explored. It does not appear that the York team were given a mandate of flexibility to identify the most suitable approach, but rather to test whether regenerative medicines could fit into the pathway developed for conventional medicines. Indeed, it seems that highly specialised technologies[16], for which NICE has created a separate assessment programme[17] (HST programme), *could* also be assessed within the TA process if necessary[18]. The question should not be whether or not it is *possible* to assess regenerative medicines by existing means, but whether or not this is *suitable*, as per the original referral.

Indeed many of the difficulties faced by HST manufacturers are also faced by manufacturers of regenerative medicines, such as limited capacity to conduct high quality RCTs, high development costs and small market size leading to high prices, and substantial parameter and decision uncertainty. The appraisal committee for the HST programme are asked to take into account the nature of the condition, the impact of the technology (including clinical effectiveness), budget impact, value for money (note this is considered to be different to cost-effectiveness: costs and QALYs are estimated but the ICER is not calculated), non-health benefits, and the impact on service delivery (for more information on the differences between the programmes see Brockis et al., 2016). This exceptional process has arisen in part due to concern that the NICE TA process, in which "the greatest gain for the greatest number" is valued highly, is unlikely to reflect true societal preferences when it comes to small vulnerable populations with rare diseases (NICE, 2013b). The NICE CAR T exercise did not consider whether or not the current TA process would allow for societal preferences around the innovative nature of these technologies, and the fact that they may provide substantial clinical gains or even cures for people living with chronic or debilitating conditions. A study to explore societal preferences in this area could be of great value.

4.4. Uncertainty and NHEs

Two of the four key conclusions reported in the NICE document (see section 3.2) relate to the decision uncertainty and the various payment mechanisms that were presented to the panel. The York report notes that the expert panel were requested to focus particularly on the role of uncertainty to: identify key areas of uncertainty, understand the nature of assessments/analyses that could help inform deliberations, and explore the impact of different pricing approaches and different evidence sets. Further, they were

[16]These are treatments for very rare conditions (so called 'ultra-orphans') that effect <1 in 50,000 people.
[17]Note that some regenerative medicines may be assessed via this route rather than the standard TA process.
[18] Arguably the NICE consultation paper (NICE and NHSE, 2016) takes a step in this direction, by introducing a maximum £100,000 threshold for NICE to approve HSTs.

presented with additional parameters to quantify uncertainty that an appraisal committee would not normally see.

The York Report uses population NHEs to illustrate: (i) total decision uncertainty, a de facto indicator of the value of perfect information; and (ii) how uncertainty changes over the lifetime of the treated patient as an indicator of irreversibility. We briefly discuss in turn the usefulness of these to the Committee.

Total decision uncertainty. The York report uses the concept of population NHEs to calculate the consequences of decision uncertainty, or, in other words, the expected value of perfect information. This is "an expected upper bound to the benefits of more research" (our emphasis) (page 185), and it does not indicate what further research can feasibly be conducted or the value that this additional research will bring (i.e. it is not the expected value of further research). It is therefore not relevant to the decision before the Committee, which is whether to: (i) approve the technology on the basis of the ICER in front of it; (ii) require additional research, either as part of a coverage with evidence development or risk sharing arrangement or as part of a refusal on grounds of lack of evidence on effectiveness or cost-effectiveness. It is not clear that the use of population NHEs in this context has been presented to the Committee correctly.

It is also worth noting that decision uncertainty, and therefore the expected value of perfect information, is likely to be substantial in the scenarios presented in the CAR T report as the ICER is very near the threshold. In addition, the expected value of perfect information will also be larger when using the £50,000 threshold than the typical £20,000-30,000 threshold for non-EoL treatments. The expert committee found the consequences of decision uncertainty to be large, and commented that it was difficult to interpret them without some sort of benchmark. The cost of conducting further research (which should, at the very least, be considered alongside the expected value of perfect information) may be high. If there are very few patients and high unmet need it may take many years to collect more evidence, making a strong case for using some other mechanism, such as coverage with evidence development and / or an innovative payment mechanism.

How uncertainty changes over the lifetime of the treated patient? The effect of this second use in the case of CAR T is to show that the NHE is negative for long periods, i.e. the NHS pays for the treatment up-front and then the benefit comes much later. The implication seems to be that this form of uncertainty is worse than (say) a situation where the *same* distribution of uncertain outcomes is derived when a patient's response (or not) is immediate. This is not strictly correct. Clearly, if large sums of money have been committed by the payer before the product is known to have long term effects, then ex post knowledge of poor effectiveness is of less value. Note, however, that there is a risk of confusion as to whether the problem is occurring at the individual patient level or at the treated population level. The problem is not only that the outcome for the first patient is highly uncertain, but that we plan to treat all existing and new patients until we know the outcome of the treatment for the first patient. It is the plan to treat other patients that is relevant in the context of a value of information calculation and can be regarded as equivalent to an irreversible commitment.

Pay-for-performance arrangements can mitigate this form of uncertainty, and we note that these are recommended for consideration.

Our analysis is predicated on our assumption that uncertainty is not relevant to decision making unless there is an option of reducing it in a way that is cost-effective, taking

account of the costs and feasibility of collecting additional data and the impact on patients of delayed access (Barnsley et al. 2016). If uncertainty is seen as an independent element of NICE decision making, then one might expect that higher uncertainty would be acceptable in circumstances of high expected health effect in patients with high unmet need.

Finally, we noted earlier that the cost-effectiveness results presented to the expert panel (see Table 3 of this report) of both the Bridge to HSTC TPP and the Curative Intent TTP show that the ICER decreases as the evidence set matures and uncertainty decreases. As we have indicated earlier and referenced in the York Report, this is an artefact of the data that has been used in this specific analysis (in particular the survival data is more favourable in the more mature data sets). Whilst a more mature dataset can reduce uncertainty there is no reason why it should systematically decrease the ICER estimate. The ICER impacts on decision uncertainty (because decision uncertainty is measured relative to the threshold) but the reverse is not the case.

4.5. Payment mechanisms

The panel were also presented with novel payment mechanisms for which ICERs are not normally calculated within the TA process. Given this focus on something usually outside of the remit of HTA, it is unsurprising that the panel took a keen interest. This is not to say that payment mechanisms are not a valuable tool for managing uncertainty, but it should be noted that these were not picked out of a vast selection of innovative proposals put to the panel. Rather, the project team selected these mechanisms. Inclusion of committee discussion around payment options as part of the NICE TA process would represent a significant departure from current process: the recommendation made by the NICE and York teams seems appropriate, that collaboration between NHS England and manufacturers will be critical for developing practical and workable payment methods for risk sharing.

We can also note however, that outcomes-based schemes are already possible under Patient Access Schemes and under Managed Access Schemes. The outcomes-based scheme in the CAR T analysis led to a lower ICER than the lifetime leasing scheme. Of course, this is not inherent but depends on the design of any pricing scheme.

4.6. Existing flexibilities within the NICE TA process

It is acknowledged in section 2.2.2 of this report that many of the issues facing regenerative medicines are faced by other technologies as well. The unique challenge for manufacturers of regenerative medicines is the increased frequency that these issues may occur, and that many may apply in combination. Where these problems have been encountered previously, NICE have built flexibility into their processes to allow for difficult characteristics.

One example is the HST programme mentioned above, where NICE recognised that their existing methods would be unlikely to generate positive recommendations for ultra-orphan technologies, and so exceptions relating to the required evidence and the decision making criteria were made. It is plausible that some regenerative medicines will be for ultra-rare diseases and thus will be assessed through the HST programme.

Another example is the EoL criteria that were developed to allow appraisal committees to accept high ICERs where certain criteria were met. The CAR T exercise indicates that the EoL criteria are likely to apply to some regenerative medicines, and thus some therapies

will benefit from this provision. Interestingly, the NICE methods guide also allows for the EoL criteria to be used in other circumstances when instructed by the NICE board (NICE 2013a). Hettle and colleagues (2016) suggest that "Further research may be warranted to determine whether a similar weighting approach might be appropriate for regenerative medicines and cell therapies". NICE does not comment on this in its report.

Within the 'standard' TA process, i.e. the EoL criteria do not apply, and the product has not been routed to HST, there are further flexibilities which may be applicable to regenerative medicines:

- **Innovation:** The innovative nature of the technology can be considered as part of the committee's deliberations, and technologies with ICERs exceeding £20,000 per QALY (the lower bound of the cost-effectiveness threshold range) may be recommended if they are considered to add benefits which would not have been captured in the cost-per-QALY estimate (NICE, 2013a). It is plausible that regenerative medicines will be considered innovative and thus may benefit from this flexibility, although Hettle et al. comment that neither of the regenerative medicines appraised by NICE to date have been considered to demonstrate such benefits (Hettle et al., 2016).
- **Non-health benefits**: This includes benefits that are considered "socially valuable" but are not captured within cost per QALY analysis. Such non-health benefits could apply to regenerative medicines, although none were noted in the CAR T exercise.
- **Weaker evidence for rare technologies:** Technologies for rare diseases are eligible to be assessed through the TA process (whilst technologies for ultra-rare diseases are assessed through the HST programme). The TA methods manual states that the committee should recognise that the evidence base will necessarily be weaker for some technologies, such as those for the treatment of very rare diseases. Hettle and colleagues (2016) comment: "If considered appropriate, this could be extended to include regenerative and cell therapies".
- **Discount rate:** as discussed previously a lower 1.5% discount rate may be applicable in some cases. It is unclear how far this is will apply to regenerative medicines; the expectation is that many will fulfil the first part of the criteria (i.e. that patient benefits will be significant and long lasting), but not the second (due to the potential for high irrecoverable costs).

One key issue that is not accounted for within NICE's existing methods, despite being faced by some medical devices (not necessarily regenerative medicines) is the issue of iterative improvements in the product. There was a case in practice where Ambu aScope2 was being assessed through NICE's medical technology guidance (MTG) programme, where a newer updated version of the device (Ambu aScope3) was released, and thus the guidance was out of date as soon as it was published (Brockis et al., 2016; NICE, 2013c). The MTG programme is intended to be a rapid process (only cost-saving devices are assessed via this process; cost-incurring devices are eligible for assessment via the TA programme), which would in theory prevent this sort of thing from happening, but in practice it appears that the challenges of iterative improvements in technologies has not been overcome.

Finally, we have noted that NICE and NHS England have released (NICE and NHSE, 2016) a consultation document which proposes some changes to the TA and HST programmes. Amongst other things, the changes suggest that for HST, therapies with an ICER below £100,000 can be funded through routine commissioning budgets (treatments

with ICERs above this threshold will be considered through NHS England's process for prioritising specialised technologies), and for TA, therapies with an ICER below £10,000 per QALY can be automatically accepted. Either of these proposed rules could theoretically apply to regenerative medicines, although due to high cost concerns (meaning that ICERs are unlikely to be below £10,000) the HST rule is more likely to be relevant for these therapies. It remains to be seen whether these changes will be implemented, and if so, the extent to which they may apply to regenerative medicines.

Clearly flexibilities exist within NICE's current methods which may be applicable to regenerative medicines. Further, the York report suggests that some of these exceptions could be extended to apply to regenerative medicines and cell therapies generally, although NICE did not comment upon these speculations. It could be helpful to manufacturers if NICE issued either an update to their methods manual or a separate summary document that outlines how each of these flexibilities are expected to apply to regenerative medicines. At present, it seems that developers of regenerative medicines will need to investigate the extent to which each individual product fits within the current flexibilities around non-health benefits, discount rates, EoL, innovation and rare or ultra-rare conditions.

4.7. Further comments

This report has focused on the key issues that may affect regenerative medicines, and how these have been addressed with NICE's CAR T exercise. It has been acknowledged that some regenerative medicines will be routed through the HST programme, and some through the TA programme. However, it is also worth noting that NICE may not assess some of these medicines at all. Indeed many drugs for rare diseases are not looked at by NICE, and instead are assessed by NHS England through their specialised commissioning services. The UK Government's Department of Health and NHS England decide which topics NICE will and will not look at, and it remains to be seen how many regenerative medicines will be evaluated by each organisation.

4.8. Areas for further research

This review of the NICE CAR T exercise has uncovered several possible areas in which additional research would be beneficial. These include:

- Further analyses which explore possible issues for regenerative medicines that were not explored through the CAR T exercise, specifically looking at the problems which may arise when the therapy requires a substantial shift in clinical practice in the NHS, has the potential for learning curve effects, and is iterative in nature, in the way that a medical device can be.
- Valuing of a cure. Further research to explore whether society values "cures" more highly (or less highly) than the sum of the iterative improvements that might come from conventional therapy, would be useful to determine whether or not additional weight should be given to QALY gains that arise from curative therapies. This research need not be restricted to regenerative medicines, as this issue is also topical in other therapy areas where cures are beginning to emerge.
- The question as to the applicability of the EoL criteria to a curative therapy. This requires exploring the conceptual basis for the EoL weighting, and looking at the extent to which that underpinning and implicit societal weighting might be displaced by a therapy that lengthens life considerably.

- Appropriate characterisation and handling of uncertainty. There appears to be a likelihood that because regenerative medicines are often more uncertain in outcome they are at risk of being seen as therefore of less value.
- Linked to this point is the need for research by NICE and NHSE in collaboration with manufacturers to develop practical and workable payment methods for risk sharing and consider other new funding and payment mechanisms, together with an exploration of how such mechanisms may affect the TA process, and require interaction between NICE and NHSE.
- The proposal in the York report for the introduction of the use of the concept of NHE requires further consideration. It is not obvious to us what benefit the proposed use of this concept brings to the appraisal process. Looking at the population NHE reinforces the importance of the relevant threshold but does not provide any new information. If the threshold is £50,000, then approving a technology with a threshold above this will lead to a negative NHE (and population NHE), because the NHE is calculated using the threshold, but it does not take into account any additional factors (such as non-health benefits, innovation) that might (or might not) warrant in the view of the Committee a treatment exceeding the "pure health gain" threshold. The use of the NHE concept to illustrate the value of perfect information is potentially misleading if the cost and feasibility of reducing that uncertainty is not set out alongside this estimate. What are the Committee expected to do with a calculation of the value of perfect information on its own? Calculating an NHE profile over time for an individual patient is interesting, but confuses the real problem, which is the *other* patients we might treat before we know if the first patient has benefited, i.e. that there are long term health gains. The point the York team are trying to make, we think, is that, if the treatment is approved more money will be invested before the uncertainty is resolved. If so, then the correct conceptual framework is by introducing irreversibilities into a value of information or coverage with evidence development calculation.
- Discounting at 3.5% or 1.5% will have a substantial effects on the value of health gains from a curative therapy. The rationale given for using 3.5%, i.e. concern about irreversibilities, appears to us to be arbitrary and irrelevant. The implication is that such effects increase uncertainty and increased uncertainty is best dealt with by using a higher discount rate. This is not technically correct.
- The potential for a mock appraisal reviewing a regenerative medicine within the HST programme. This might require the use of more structured decision making processes (Thokala et al., 2016; Marsh et al., 2016) to consider trading off the various elements, of which the cost-per-QALY is only one.

5. CONCLUSIONS

Hettle and colleagues (2016) conducted several detailed literature reviews looking at the key issues that may be faced by regenerative medicines, and undertook a thorough and informative mock appraisal of CAR T-cell therapy. Due to the nature of regenerative medicines covering a wide spread of technologies, in combination with additional practical constraints, the team were unable to pick a technology that faced all the possible issues that may be faced by regenerative medicines. As a result, not all of the key issues were explored within the exercise.

The CAR T exercise did not seek to identify the most suitable approach for assessing regenerative medicines, but rather to test whether regenerative medicines could fit into

the existing pathway developed for conventional medicines. NICE then concluded that they do, with the implication that this means the current methods are fit for purpose. We note that many (if not all) technologies, including those which are currently assessed via the HST programme, *could* be assessed within the TA process if necessary, but they are not necessarily required to do so. The question should not be whether or not it is possible to assess regenerative medicines by existing means, but whether or not this is suitable, as per the original referral.

Where regenerative medicines offer substantial benefits to patients it is important that the TA process does not act as a 'blocker', for example where difficulties in conducting large scale RCTs amongst severely ill populations leads to substantial decision uncertainty and prevents a committee from making a positive recommendation. Yet, on the other hand, any significant departures from the usual TA process must be based on solid economic rationale if we are to ensure efficient allocation of NHS resources. This report has acknowledged that many of the key issues likely to be faced by regenerative medicines are not unique to these technologies. The unique problem is that these medicines are likely to face a higher concentration of these problems.

Some flexibilities do exist within the current NICE process (such as differential discount rates where substantial benefits are expected long term, inclusion of non-health benefits in particular circumstances, acknowledgement of weaker evidence where it is difficult to conduct full RCTs), and as such it seems reasonable to conclude that many regenerative medicines will be adequately assessed within NICE's current programmes (the expectation is that some will be routed through the TA process and some through the HST programme; some may not be seen by NICE at all). Still, there is a lack of clarity and consistency in how committees apply these flexibilities, and regenerative medicines are likely to meet problems at the extremes, such as when substantial decision uncertainty hinders the decision making process, or when substantial clinical benefits (or cures) are offered at very high cost. It would be helpful if NICE could issue either an update to their methods manual or a separate summary document that outlines how each of these flexibilities are expected to apply to regenerative medicines.

Further research into risk sharing and other innovative financing mechanisms and the true value of a cure will shed light into the appropriate way to tackle these problems. The York team also made some suggestions on how the current TA process could be modified. NICE have committed to exploring the quantification of uncertainty, but have not commented within the current report on if and how they plan to take the other suggestions forward. We have proposed a series of areas where additional research would be helpful in clarifying issues raised by the York and NICE reports.

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