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

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Produced by CRD and CHE Technology Assessment Group, University of York, Heslington, York YO10 5DD

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1 Plain English summary

The assessment of the clinical- and cost-effectiveness of regenerative medicines may raise particular challenges compared to assessments made of other types of technologies. The aim of this project is to test the application of NICE appraisal methodology to regenerative medicines and cell therapies, identifying challenges and areas where changes to methods or research is needed. This will be done using a pretend technology (based on CD19 CAR T cell therapy). It will include analysing hypothetical data sets to represent three different levels of evidence, which will reflect the different levels of completeness/ robustness of the evidence likely to be available in a NICE appraisal. The study report will help NICE decide if changes to their methods are needed to deal with regenerative medicines. It will also inform the development of a framework for those developing regenerative medicines to help their understanding of how NICE evaluates clinical- and cost-effectiveness.

2 Project Objectives

Background

The term regenerative medicine (RM) refers to a field of research and clinical applications dealing with the process of replacing or regenerating human cells, tissues or organs to restore or establish

normal function.[1] Regenerative medicine encompasses cell-based therapies (often using stem cells or progenitor cells to produce tissues), gene therapy, and tissue engineering.

A report of the House of Lords Science and Technology Committee's inquiry into regenerative medicine was published in July 2013. This called for a regenerative medicine expert working group to be established to develop an NHS regenerative medicine delivery readiness strategy and action plan, and report back to the Secretary of State for Health by December 2014.[2] In response to this the Regenerative Medicine Expert Group (RMEG) was convened and was given the remit to monitor progress on the Government's response to the House of Lords inquiry; and to develop, in partnership with other stakeholders, a strategy for regenerative medicine in the NHS and provide an action plan. In its report[3] the RMEG stated that,

"In order for NHS patients to benefit from regenerative medicines, robust and effective product evaluation has to be made to inform commissioning decisions. National Institute for Health and Care Excellence (NICE) guidance is essential in speeding up the adoption and spread of high value regenerative medicines in healthcare. However, applying the Institute's appraisal methodology, based on cost utility analysis, to products whose true value may not be known for many years can be challenging, due to the inherent uncertainty of estimating long-term benefit from evidence derived from short-term studies."

The assessment of the cost-effectiveness of regenerative medicines may raise particular challenges compared to other types of technologies. Important challenges may include: the potential curative nature and claims of long-term /lifetime benefits; the potentially rapid changes that may arise in product characteristics over time; potential longer-term patient safety issues due to persistence; organisational and scaling issues, as well as the potentially significant up-front costs that may arise. Whether the conceptual differences between regenerative medicine and other types of technologies (e.g. pharmaceuticals and medical devices) require a different approach to the conduct and assessment of cost-effectiveness needs to be investigated.

The RMEG Evaluation and Commissioning Subgroup proposed that NICE commissions a "mock technology appraisal" on exemplar regenerative medicine products and developed an outline plan for such a study. This proposal was reflected in the final report and recommendations of RMEG[3], which stated further,

"We encourage the Institute to consider the findings from these studies with a view to assessing whether changes to its methods and processes are needed. Evaluation and commissioning, as with all

steps of the product development pathway, need to be supported by clear, up-to- date and accessible advice and guidance. "

Through RMEG subgroup discussions and further input from the Cell Therapy Catapult, it has been concluded that undertaking a study involving a real commercial product is not feasible for a number of reasons: there would be significant commercial sensitivities; products undergoing regulatory review would be a candidates for a real appraisal; and using a product at an earlier stage in clinical development is not helpful as the evidence base would be even less mature and, therefore, it would not have the attributes of an 'exemplar' product. It was therefore proposed to undertake the evaluation of a hypothetical product.

The NICE Board approved the study on the basis of the project outline which sets out the objectives of the study, some of the key issues that will need to be considered and presents an outline plan for delivery of the work (See Appendix 1). The objectives of the study are:

- 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.

3 Methods for investigation of the clinical evidence

This part of the project will comprise two distinct but interdependent elements:

- Development of the target product profile and three evidence sets for the hypothetical product as the basis for the exemplar appraisal
- A broader exploration of the applicability of NICE TA methods to regenerative medicines using the current NICE appraisal process and decision framework

3.1 Target Product Profile (TPP)

From RMEG subgroup discussions, the lead candidate for the hypothetical product is in the area of T cell therapy for the treatment of leukaemia. This is because there are a number of products in

development, and, for some T cell therapies in leukaemia, there are clinical trial data available along with early QALY gain estimates and cost data on alternative treatments in current use.

Early discussions arising from this study's first technical meeting resulted in the selection of chimeric antigen receptor (CAR) T cell therapies specific to the antigen CD19 as the hypothetical intervention, with acute lymphoblastic leukaemia (ALL) as the indication. This specific combination was selected based on the existence of relatively mature data sets (compared with other T cell therapies for leukaemia).

Developing the Target Product Profile

A meeting between the Academic Group and a sub-group of the project advisory group(topic experts) was held on 23rd April 2015, where the CAR T cell clinical data were presented and discussed, and key aspects of the TPP agreed. The agreed components of the TPP were:

Intervention: CD19 CAR T cell therapies

Indication: 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 to standard chemotherapy

Subgroups: Sources of heterogeneity such as relapsed/refractory status, previous HSCT, CAR design, dose, conditioning chemotherapy, tumour burden at the time of therapy, or age of the patients may be explored.

Comparators: Best supportive care (e.g. salvage chemotherapy)

Efficacy outcomes: Response criteria such as complete response/remission (CR), partial response/remission (PR), and minimal residual disease negative (MRD); overall survival (OS); progression and/or event-free survival; persistence of CAR T cells; health-related quality of life; rates of HSCT

Adverse event outcomes: Cytokine release syndrome (CRS), B-cell aplasia, febrile neutropenia, neurologic effects

The TPP will also encompass study design issues such as the clinical or ethical/practical justifiability of the sample sizes and outcome measures used, and the lack of comparator arms. Any further study quality issues seen in the B-ALL CAR T cell trials - such as the external validity and applicability of results - will also be noted to help inform a broader exploration of the applicability of NICE appraisal methods to RMs (see section 3.2). The developed TPP will be presented and discussed at a meeting of

the full Project Advisory Group (see Appendix 2) on 24th June 2015 and if necessary will be modified according to the result of that discussion.

New technologies come to licence application and NICE appraisal at various stages of development of the supporting evidence base. To explore the impact of different levels of completeness/ robustness of the evidence base, hypothetical data sets representing three different anticipated evidence set scenarios will be constructed:

- Early (minimum evidence required for conditional marketing authorisation)
- Intermediate (target)
- Mature (optimistic)

The data used will vary in magnitude and/or precision across scenarios and will be a reflection of data characteristics such as:

- Duration of follow-up: very short-term follow up to follow up of several years
- Level of evidence: small, single-arm studies to appropriately powered RCTs
- Types of outcome available: short-term surrogate outcomes (e.g. CR) to longer-term optimal clinical outcomes (e.g. OS)
- Adverse effects (AEs): uncertain or unpredictable AEs to reasonably well understood AEs
- Curative potential and durability of effect
- Evidence on Health related Quality of Life
- Heterogeneity of population recruited
- Heterogeneity of doses used (in dose-escalation studies)

Data to inform the TPP will be derived both from CD19 CAR T cell trials, and from other types of study in B-ALL populations. The published clinical trial data available for CD19 CAR T cells in ALL, has been identified by staff at Cell Therapy Catapult (who comprise part of the project Advisory Group, being experts in cell-based regenerative medicines). This evidence was reviewed by the Academic Group and was used to inform the basic TPP above.

This evidence will be expanded upon, using update searches of Medline and Embase, which will be conducted to identify any further relevant clinical trials, and experts will be contacted regarding relevant 2015 conferences where new data may have been presented. To further inform what data might be anticipated, ongoing trials of CD19 CAR T cell in ALL will be searched for on the ClinicalTrials.gov trials registry and recent non-regenerative medicine therapy EMA approvals for refractory or relapsed ALL will be examined. Clinical advice will also be sought. The trial data will be synthesised: trials will be pooled where clinical heterogeneity does not preclude this, or data

adjusted to better match the modelled population. Efforts will be made to avoid the hypothetical data sets reflecting exactly the data for any real CAR T cell technology.

To identify evidence on further aspects of B-ALL necessary to construct the three hypothetical data sets, reviews of studies in the following areas will be undertaken:

- The natural history of late relapsed/refractory B-ALL
- The relationships between short-term surrogate outcomes (e.g. complete response, MRD^-) and longer-term, intermediate and/or final outcomes (e.g. progression-free/ event-free survival and overall survival in B-ALL
- Health-related quality of life in late relapsed/refractory B-ALL
- Methods on how bias arising from study designs might be minimised, and methods to quantify the direction and/or magnitude of potential biases and possible approaches to adjustment

As this is an appraisal exercise rather than a full appraisal, standard systematic review methods will not be appropriate. A pragmatic approach will be adopted, with basic methods being used (e.g. for the searching and screening of studies, only MEDLINE and Embase will be searched, with references screened by one reviewer). Studies will also be sought from any existing systematic or adequately objective reviews, and from publications already known or identified by clinical advisors.

In order to prevent presentation of commercially sensitive results, the CD19 CAR T cell B-ALL trials will be anonymised, and data will also be pooled where possible. Furthermore, it is not anticipated that the actual trial data currently available will be directly used as the sole basis for informing any of the three data sets.

The trial data will be modelled, incorporating prognostic factors, surrogacy factors and bias factors, and increased sample sizes simulated as necessary in order to generate the three hypothetical data sets. The precise methods to be employed depend upon the findings of the reviews listed above.

3.2 A broader exploration of the applicability of NICE TA methods to regenerative medicines: Clinical evidence issues

In the first instance a review will be undertaken of regenerative medicines previously appraised under NICE technology assessments. These include autologous chondrocyte implantation for repairing symptomatic articular cartilage defects of the knee,[4] and sipuleucel-T for the first line treatment of metastatic hormone relapsed prostate cancer.[5] EMA reports of evaluations of RMs will also be examined for methodological issues: Glybera (gene therapy for lipoprotein lipase deficiency, 2012); Chondrocelect 2009 and MACI 2013 for knee cartilage defects; Provenge cell therapy for prostate

cancer (2013) and Holoclar for severe limbal stem cell deficiency (2015). NICE appraisals in non-RM therapies may also be considered where similar issues (to those associated with RM) may exist.

An assessment of any further likely RM study design issues (some of which were outlined in section 3.1) will then be undertaken. Discussion will be made of how the issues listed below may relate to attainment of product licenses and the impact in terms of 'evidence-based medicine', i.e. identification of the true treatment effect and the precision of the estimate (reduced uncertainty).:

- Lower level of evidence: single arm studies rather than appropriately powered RCTs
- Surrogate outcomes rather than intermediate and/or final clinical outcomes
- Evidence for durability of effect
- Potential for RMs to effect a cure
- Adverse effects data: Uncertain (unpredictable?) adverse effects
- Evidence on Health related Quality of Life – always very limited with drugs, likely to be much more so with RMs
- Duration of follow-up – again, often limited with conventional technologies, but likely to be much more so with RMs (lack of long term evidence of real 'cure' or durability of effect)

Consideration and discussion will also be made of how these issues might impact on approaches to the evaluation of clinical effectiveness in the context of the technology appraisal process (e.g. such as how best to quality-assess, and synthesise data from single-arm studies). This list of issues will be discussed at the meeting of the Project Advisory Group (see Appendix 2) on 24th June 2015 and if necessary will be modified according to the result of that discussion.

To inform this work, key methods publications and documents will be sought from sources such as the NICE, HTA, GRADE and FDA websites, and The Cochrane Library. The information found will be supplemented by citation searching for further relevant publications.

4 Methods for investigation of the Cost effectiveness

Some of the issues associated with regenerative medicines will inevitably impact on the level of uncertainty associated with the cost-effectiveness of the technology when introduced into clinical practice. Even where products have significant potential to confer important clinical advances over current therapies, this may not be known with a high level of certainty at the time a regenerative medicine is licensed. Inevitably a new technology's cost-effectiveness may be more difficult to determine in these circumstances and schemes that allow the development of further evidence or entail a risk-sharing component might be required.

This general issue of balancing the value of additional evidence about the performance of the technology and the value of access to the technology is central to a number of important policy questions in many different types of healthcare systems. Consequently, one of the main methodological challenges arising from this is how uncertainty should be characterised in these circumstances and how policy makers should appropriately respond. Managed entry agreements (MEAs) are an increasingly common policy response to dealing with uncertainty in the evidence base of new health technologies entering the market. MEAs are also commonly referred to as performance-based risk sharing agreements (PBRSAs) and patient access schemes (PASs). How to estimate the potential value of a new technology under conditions of uncertainty and quantify the value of future research, is thus a key methodological issue that has important implications for both policy making and research investments made by the regenerative medicine industry.

The main objectives of the proposed work pertinent to the cost-effectiveness of regenerative medicines are:

- To identify the key assessments needed to inform policy decisions for regenerative medicines related to: (i) value (cost-effectiveness); (ii) decision uncertainty and (iii) value of conducting further research.
- To examine the extent to which assessments of cost-effectiveness and uncertainty may differ between regenerative medicines and other health technologies
- To examine the relevance of existing frameworks for health technologies and identify potential challenges and/or areas where further methods research and/or adaptation of methodology maybe appropriate

These objectives will be informed by a series of related tasks. These include:

- Task 1: Focused scoping exercise to identify potential conceptual differences between regenerative medicines and conventional health technologies;

- Task 2: Development of exemplar economic model;
- Task 3: Assessment of cost-effectiveness and uncertainty and the value of alternative policy options
- Task 4: Further exploratory work. The different elements of work proposed within each of these tasks are outlined below.

4.1 Task 1: Focused scoping exercise to identify potential conceptual differences between regenerative medicines and conventional health technologies

The cost-effectiveness elements of the project will start with a focused scoping exercise to help to identify potential conceptual differences between regenerative medicines and other conventional technologies. The objective of the scoping review will be to identify the potential characteristics of regenerative medicines which could make any assessment of cost-effectiveness, uncertainty and the value of further evidence different from other technologies. These characteristics will then form the basis for subsequent exploratory work to assess the appropriateness of existing decision frameworks for health technologies. The goal of this work is to identify areas where additional methodological development may be required.

The scoping review will be based on general issues for regenerative medicines reported in existing cost-effectiveness literature[6, 7] and specific consideration of previous and ongoing NICE Technology Appraisals for other regenerative products. These include: TA332: Sipuleucel-T for treating asymptomatic or minimally symptomatic metastatic hormone-relapsed prostate cancer and ID686: Knee cartilage defects - autologous chondrocyte implantation. The scoping review will focus on the following issues: expected cost-effectiveness of regenerative medicines; sources of uncertainty; whether additional research is possible; benefits of additional research; significance of irrecoverable costs; pricing for existing regenerative medicines; issues surrounding the implementation of NICE guidance, and anticipated changes over time (e.g. emergence of new evidence or comparators, changes in price etc.).

The output of this stage will be a summary of areas where conceptual differences between regenerative medicines and more conventional technologies may exist to help identify any additional assessments that may be required. These will be presented to the Project Advisory Group (PAG) in June. The results of the scoping exercise, together with feedback and comments received from the PAG, will then be used as the basis for developing the exemplar model (Task 2) and associated exploratory analyses (Task 3). Through the exemplar case-study, these exploratory analyses will consider the appropriateness of NICE appraisal methodology and related frameworks which have

been proposed to inform policy choice regarding conditional coverage and evidence development decisions for conventional health technologies

An important consideration will be the extent to which the exemplar application, based on the proposed TPP and hypothetical evidence sets, will be sufficiently generalisable (i.e. the extent to which the key conceptual differences are evident in this specific application) to inform the broader objectives of the project. Consequently, an additional more exploratory stage of work is also proposed (see Task 4) which will be based on a series of 'stylistic' adaptations of the exemplar model to enable a broader set of issues to be considered which may allow more generalised conclusions to be made.

4.2 Task 2: Development of exemplar economic model

Model conceptualisation stage

A focused review of existing cost-effectiveness studies in B-ALL will be undertaken as part of the initial model conceptualisation stage. A systematic search will be undertaken using NHS Economic Evaluation Database (NHS EED). The final records were added to NHS EED in January 2015. A separate search for 2015 will thus be undertaken using Medline and EMBASE. This will also be supplemented by a separate search of the NICE website to identify any previous technology appraisals or clinical guidelines in the proposed indication.

Based on the results from the systematic search, a focused review will be undertaken to examine existing decision-analytic models, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from these existing models. This review will be used to identify key issues associated with adapting existing decision model structures to address the exemplar case-study and to inform the subsequent development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

The results from this review, alongside the clinical and epidemiological evidence identified as part of the clinical reviews, will be used to develop a provisional model structure and key assumptions that will be required. This will then be discussed with the EAG in June to ensure that the model and assumptions appropriately characterise the disease processes and the anticipated clinical effects of the hypothetical product.

Model development stage

A new decision-analytic model will be developed to estimate the cost-effectiveness of the product based on the hypothetical evidence sets. The model will be developed in accordance with the current NICE reference case. The model will have a lifetime horizon. Outcomes will be expressed in terms of

quality-adjusted life years (QALYs) and costs will be assessed from the perspective of the National Health Services and Personal Social Services.

The specific objectives are to:

- To structure an appropriate decision model to characterise patients' care and subsequent prognosis and the impacts of the product.
- To populate this model using the separate hypothetical evidence sets (see Section 3.1) and to incorporate any additional clinical and economic data required. It is anticipated that the evidence used to generate the TPPs and the hypothetical evidence sets will be sufficient to inform the key clinical and epidemiological parameters of the model. However, depending on the final model structure, additional evidence may be required and pragmatic approaches will be followed to identify relevant sources (e.g. targeted reviews, routine data sources, expert opinion).
- To relate initial and intermediate outcomes (such as response to treatment) to final health outcomes, expressed in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by each intervention, relative to its additional cost, in units which permit comparison with other uses of health service resources.
- To characterise the uncertainty in the data used to populate the model and to present the uncertainty in these results to decision makers. A probabilistic model will be developed which requires that each input in the model is entered as an uncertain, rather than a fixed, parameter. Using Monte Carlo simulation, this parameter uncertainty, is translated into uncertainty in the overall results. This ultimately helps decision makers understand the probability that, in choosing to fund an intervention, they are making the correct decision – that is, decision uncertainty. This is presented using cost-effectiveness acceptability curves which show the probability that each intervention is cost-effective conditional on a range of possible threshold values which NHS decision makers attach to an additional QALY.

4.3 Task 3: Assessment of cost-effectiveness, uncertainty and the value of alternative policy options

The TPP and alternative hypothetical evidence sets will be used to generate assessments of the cost-effectiveness, decision uncertainty and to demonstrate the potential value of alternative policy options. The alternative hypothetical evidence sets will be used to explore the potential impact of different levels of evidence on these assessments and on the committee decision making process. The objective will be to investigate the appropriateness of existing approaches and to identify areas where additional analyses and/or further advances in methodology may be required.

This element of work will be based on assessments using existing NICE methodology and the types of analyses conventionally undertaken, as well as considering any additional analyses that could be provided to help inform the committee's decision making. In particular, consideration will be given to the relevance of the general framework for health technologies recently developed to inform policy choice regarding conditional coverage and evidence development decisions[8] and work being undertaken by the NICE Decision Support Unit on "Methods for the Assessment of Performance Based Risk Sharing Schemes within the NICE Technology Appraisals Programme".

A key element will be in exploring how uncertainty (both parameter and structural) in the evidence could be appropriately characterised and subsequently represented to the Appraisal Committee. Conventional sensitivity and scenario analyses will be undertaken to demonstrate the impact of cost-effectiveness (i.e. based on alternative extrapolation assumptions and applying discount rates). However, it is likely that some of the key uncertainties may be associated with assumptions and judgements that may be difficult to quantify using conventional approaches. In these circumstances, we will explore the feasibility of applying methods such as expert elicitation and model averaging to represent forms of structural uncertainty.

In the absence of a known acquisition cost of the hypothetical technology, separate analyses will be undertaken based on different pricing scenarios. Threshold analysis will also be undertaken to highlight the relationship between price and subsequent assessment of cost-effectiveness, uncertainty and the value of alternative policy options.

4.4 Task 4: Further exploratory work

A series of more exploratory analyses will be undertaken based on the exemplar case study. These analyses will include: (i) an exploratory analysis of alternative MEA/PBRSA scenarios and (ii) stylistic extension of the case-study to illustrate more general issues which may not be captured in the case-study.

Exploratory analysis of alternative MMEA/PBRSAs scenarios

As previously highlighted, MEAs/PBRSAs are an increasingly common policy response to dealing with uncertainty in the evidence base of new health technologies entering the market. While the analyses undertaken in Task 3 provide a basis for which the value of different policy options could be quantified, it will also be important to demonstrate how these assessments may be impacted by different risk-sharing approaches which could also be proposed by the manufacturer. Indeed, exploring how the assessments of cost-effectiveness, uncertainty and the value of alternative policy options might be affected under different proposed MEAs/PBRSAs could provide a valuable insight for manufacturers in prospectively identifying the likely need for and design of such schemes.

A series of additional exploratory analyses will be undertaken to consider how assessments of cost-effectiveness, uncertainty and the value of subsequent policy options could be impacted by MEAs/PBRSAs. The analyses will consider schemes that are based primarily on further evidence generation activities as well as more innovative approaches to pricing (e.g. leasing type approaches) which have been suggested as a potential risk-sharing approach in relation to the potential challenge of high upfront costs.[6, 7]

Stylistic extension of the case study

There are several features of the proposed exemplar application (i.e. oncology based, small-population) which are anticipated to raise potential challenges in demonstrating the potential issues with current approaches to assessing cost-effectiveness and uncertainty. Given resource and time constraints, undertaking additional case studies is not considered feasible. However, consideration will be given to whether through stylistic extension of the case study, issues and challenges general to regenerative medicines more broadly might be demonstrated. We therefore propose to use the case study as vehicle to demonstrate more generalised issues. We consider that simple amendments to the model and/or inputs (e.g. increasing population size, altering survival functions to simulate a more chronic type disease, eliminating survival differences and considering only quality of life effects) could provide valuable additional insights and more generalised learning.

5 Exemplar Appraisal

Reports of the work outlined in Sections 3 and 4 will be submitted to NICE. The NICE technical team will set up a panel comprising around 10 experts with a strong understanding of NICE Technology Appraisals, including members with experience of serving as Committee members. Using the submitted report, the panel will consider each TTP / hypothetical evidence set combination and indicate the recommendations that would be most likely to be developed. The panel will also provide commentary on issues related to methods or decision frameworks that could address challenges of evaluating regenerative medicines and cell therapies.

6 Project stages and timelines

The project will be undertaken over an 8 month period, beginning in April 2015:

Activity	**Duration/completion dates (2015)**
Protocol development	April (including meeting with subgroup of Project Advisory Board 23/04/2015)

Cost-effectiveness scoping exercise	April - June
Meeting with Project Advisory Board	24/06/2015
Development of TPP and hypothetical evidence sets	April - July
Development of exemplar economic model Model conceptualisation stage Model development stage	April - September April - June April - September
Assessment of cost-effectiveness, uncertainty and the value of alternative policy options	July - October
Further cost-effectiveness exploratory work	September - November
Exploration of the applicability of NICE technology appraisal methods to regenerative medicines (trial/study design issues)	July - September
Submit draft report	September 2015
Submit final report	November 2015

7 Project team

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The team are part of the York TAR team who hold a contract to undertake health technology assessment reports for NICE. Nerys Woolacott and Stepehen palmer have led this team for 10 years. Stephen Palmer will lead the evidence synthesis and modelling components of this work, with experienced Health Economists, Sebastian Hinde and Robert Hettle. Nerys Woolacott will lead the review elements of this work, with experienced researchers Mark Corbett, Robert Hodgson, Julie Jones-Diette. And.

8 Competing interests of authors

None

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10 Appendices

Appendix 1 – Outline Project Plan

Regenerative Medicine Expert Group (RMEG)
Evaluation and Commissioning Subgroup

Study exploring the assessment and appraisal of regenerative medicines and cell therapy products

Outline Project Plan

Background

1. The RMEG Evaluation and Commissioning Subgroup proposed that NICE commissions a "mock technology appraisal" on exemplar regenerative medicine products and developed an outline plan for such a study. This proposal was reflected in the final report and recommendations of RMEG.

2. A route for funding part of this work through NIHR Evaluation, Trials and Studies Coordinating Centre (NETSCC) was identified and the Centre for Reviews and Dissemination, University of York has been assigned to this project.

3. The NICE Board approved the study on the basis of the project outline below which has not been substantially modified from the version developed by the RMEG Evaluation and Commissioning subgroup. The term "mock technology appraisal" was considered potentially confusing and not reflective of the study proposed and the study title above adopted.

4. This project outline sets out the objectives of the study, some of the key issues that will need to be considered and presents an outline plan for delivery of the work.

Objectives

5. The key objectives of the study are:

    - 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.

6. Through RMEG subgroup discussions and further input from the Cell Therapy Catapult, it has been concluded that undertaking a study involving a real commercial product is not feasible because

    - There would be significant commercial sensitivities
    - A study involving a product that is undergoing regulatory review would not be feasible as it would be a candidate for a real appraisal
    - Using a product at an earlier stage in clinical development is not helpful as the evidence base would be even less mature and, therefore, it would not have the attributes of an 'exemplar' product.

7. It is therefore proposed to undertake the evaluation of a hypothetical product. The attributes of the hypothetical product will be developed based on a Target Product Profile. The Target Product Profile will include anticipated key clinical and cost outcomes compared to current standard of care (e.g. extension to length of life, quality of life, impact on NHS resource use, product cost) and will be defined based on the available clinical trial data for actual products in related areas and expert input.

8. One of the major discussion areas at the RMEG subgroup was that, even where products have real potential to be clinically effective, this may not be known with a high level of certainty at the time an ATMP first comes to market. Exploring the impact of a limited evidence base on the decision options will be a major consideration of this study. To explore this, it is proposed to consider the Target Product Profile as the value proposition claimed for the product and produce a number of hypothetical evidence sets that reflect the levels of evidence that may be available to support the Target Product Profile. An evidence set could be devised to reflect the minimum level of evidence that would allow an ATMP to receive a marketing authorisation and other evidence sets could be devised that were illustrative of higher levels of evidence from longer periods of clinical use. The impact of the different levels of evidence on the NICE appraisal process and committee decision making could then be explored. An understanding of which types of uncertainty can be reasonably addressed in an appraisal and which cannot, should be an important outcome of this work and this understanding may be generalisable to other technology areas

9. A specific issue discussed during the RMEG subgroup meetings was the discounting rates to be applied. This was considered important as regenerative medicines are

expected to be expensive but with benefits over potentially very long periods, sometimes with the potential for cure.

10. Due to this potentially curative nature of regenerative medicine products, it is anticipated that claims of long-term benefits will often be made at launch in the absence of long-term data. It is therefore important to identify the most robust and credible approaches for extrapolating long-term health-related effects of these products. We propose that the study should include the opportunity to apply and critically appraise various extrapolation methodologies for substantiating the long-term health claims of regenerative medicine products leading to an identification of the most credible methods.

Exemplar Product(s)

11. From RMEG discussions to date, the lead candidate for the hypothetical products is in the area of T cell therapy for the treatment of leukaemia. There are a number of products in development. Additionally, for some T cell therapies in leukaemia there is clinical trial data available along with early QALY gain estimates and cost data on alternative treatments in current use. There is, therefore, some basis for deriving the Target Product Profiles and the evidence sets can be based on a combination of real clinical data from early studies supplemented with hypothetical evidence. These products also have potential for use as both early and late stage treatments. It is proposed to explore both of these uses as the treatment pathway impacts may be very different in these two applications.

Outline Plan

12. The major components of the study are shown in the following table.

	Activity	**Responsibility and Indicative Timescale**
1	Appoint academic group to work on study	NETSCC with input from NICE Completed. York group available from April 2015 with limited time for preparatory work before then.
2	Establish a project advisory group comprising experts in regenerative medicine from industry and academia, HTA, ATMP regulation and leukaemia. Appoint a Chair of the advisory group to act as a key point of contact for the academic group	RMEG evaluation and commissioning subgroup January 2015
3	Further define the T cell therapies in early and late stage leukaemia treatments as the exemplar products and applications	Academic group and project advisory group January – February 2015

4	Develop Target Product Profiles for the T cell therapies in both the early and late stage applications informed by the literature available and inputs from the project advisory group. The Target Product Profiles to be reviewed by the project advisory group	Academic group April – September 2015
5	Considering the Target Product Profiles as value propositions claimed for the product, devise 2-3 hypothetical evidence sets that would be used to support the claims. One should reflect the minimum data that is likely to be available from trials to support ATMP marketing authorisation and others should reflect more robust evidence from longer use. The evidence sets should include real data where available, supplemented by hypothetical evidence where real data is not available The evidence sets to be reviewed by the project advisory group.	Academic group April – September 2015
6	Apply, modify or develop health economic model structures for the early and late stage leukaemia applications	Academic group April – September 2015
7	Model the cost effectiveness of the product in each application. Perform sensitivity analysis on the major elements of the TPP to illustrate how these impact cost effectiveness. Also model the impact of different discounting rates	Academic group April – September 2015

8	Considering the Target Product Profiles as value propositions based on evidence and assumptions, consider the extent to which the hypothetical evidence sets support the value propositions. Model the uncertainty for each of the hypothetical evidence sets. For the early stage leukaemia application, this should include consideration of the most appropriate methods for extrapolating long term patient outcomes from short term trial data.	Academic group April – September 2015
9	Prepare a draft report covering all the above areas of the study. The report should have sufficient detail to support decision making in the same way that HTA reports for NICE normally do. It should also be written with a broader audience of regenerative medicine stakeholders in mind and take particular care to ensure that the information is presented clearly and well indexed.	Academic group April – September 2015
10	Set up a panel comprising around 10 experts with a strong understanding of NICE Technology Appraisals, including members with experience of serving as Committee members. Using the report from 9 above, the panel will consider each TTP / hypothetical evidence set combination and indicate the recommendations that would be most likely to be developed. The panel will also provide commentary on issues related to methods or decision frameworks that could address challenges of evaluating regenerative medicines and cell therapies.	NICE October 2015
11	Prepare a final report including key points from the expert discussion and a section on overall learning from the exercise and any areas where methods development should be considered. This should include commentary relating to the key objectives in Section 4 above and detailed consideration of which uncertainties can and cannot be addressed at the time of appraisal. The project advisory group should be consulted prior to finalising the report.	Academic group with input from NICE November 2015
12	Prepare report for SMT and Board approval with recommendations as appropriate	NICE December 2015

Appendix 2 - NICE Appraisal of Regenerative Medicine Working Group

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Natalie Mount	Chief Clinical Officer, Cell Therapy Catapult
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Robert Hettle	CHE, University of York
Bob Phillips	Senior Clinical Academic, CRD, University of York
Ian McKay	Department of Health
Jeremy Powell	NICE
Nick Crabb	NICE
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Robert Hawkins	Cancer Research UK Professor, University of Manchester
Panos Kefalas	Head of Health Economics and Market Access, Cell Therapy Catapult
Matthew Taylor	Director York Health Economics Consortium, University of York
Philip Newsome	Professor of Experimental Hepatology, University of Birmingham
Chris Mason	Professor of Regenerative Medicine Bioprocessing, UCL
Angela Blake	Pfizer
Andrew Webster	Director of the Science and Technology Studies Unit
Paul Catchpole	ABPI
Michael Hunt	ReNeuron
Siobhan Connor	BUPA
Holger Mueller	Cell Medica
Ahmed Syed	NHS England