NIHR | Innovation Observatory

HEALTH TECHNOLOGY BRIEFING SEPTEMBER 2021

Ciltacabtagene autoleucel for relapsed and refractory multiple myeloma

NIHRIO ID	30273	**NICE ID**	10529
Developer/Company	Janssen-Cilag Ltd	**UKPS ID**	655361

Licensing and market availability plans	Currently in phase III clinical development.

SUMMARY

Ciltacabtagene autoleucel is in clinical development for the treatment of adults with relapsed and lenalidomide-refractory multiple myeloma (MM). MM is a rare, incurable cancer of the plasma cells in the bone marrow. Abnormal plasma cells interfere with the production of red and white blood cells as well as platelets, causing symptoms such as bone pain and fragility, weakness, unusual bleeding (from the gums and nose, as well as heavy periods) and eventually kidney damage. In the early stages, MM is symptomless, then, as disease progresses, patients experience periods of time without symptoms followed by periods where the symptoms return (relapsed MM). Eventually the periods without symptoms will shorten and the illness will become immune to the treatment (refractory MM). As most patients experience serial relapse to existing treatments, there is a need for new treatment options.

Ciltacabtagene autoleucel is a type of gene and cell therapy that targets a protein called BCMA (B cell maturation antigen) which is expressed on B-cells (a type of immune cell). Binding of ciltacabtagene autoleucel to BCMA prevents B-cell maturation and differentiation into plasma cells. It is administered as an intravenous infusion and aims to kill cancer cells by harnessing the power of a patient's own immune system. If licenced, ciltacabtagene autoleucel would be the first BCMA targeted CAR-T cell therapy with two distinct antigen binding domains for MM.

PROPOSED INDICATION

Treatment of adults with relapsed and lenalidomide-refractory multiple myeloma (MM).[1]

TECHNOLOGY

DESCRIPTION

Ciltacabtagene autoleucel (JNJ-4528, JNJ-68284528, LCAR-B38M) is a preparation of autologous T-lymphocytes. They are transduced, *ex vivo*, with a lentiviral vector expressing a chimeric antigen receptor (CAR) containing two bispecific anti-B-cell maturation antigen (BCMA) variable fragments of llama heavy-chain murine antibodies fused to the signalling domain of 4-1BB (CD137). Ciltacabtagene autoleucel has potential immune-stimulating and antineoplastic activities. The antigen-binding region of the CAR is a non-scFv structure targeting two distinct regions of BCMA. Upon intravenous (IV) administration back into the patient, the autologous BCMA-targeted CAR T-cells ciltacabtagene autoleucel are directed to cells expressing BCMA, bind to two different epitopes on BCMA and induce selective toxicity in BCMA-expressing tumour cells. BCMA, a tumour-associated antigen (TAA) and a receptor for both a proliferation-inducing ligand (APRIL) and B-cell activating factor (BAFF), is a member of the tumour necrosis factor receptor superfamily (TNFRSF) and plays a key role in plasma cell survival. BCMA is overexpressed on malignant plasma cells.[2,3]

In the phase III clinical trial (CARTITUDE-4, NCT04181827) participants will receive ciltacabtagene autoleucel infusion 0.75 * 10^6 CAR-positive viable T-cells/ kilogram (kg).[1]

INNOVATION AND/OR ADVANTAGES

As MM is an incurable malignancy, new approaches to treatment are needed. T-cell therapies are a promising approach for treating MM, with a mechanism of action different than those of standard MM treatments. CARs are fusion proteins incorporating antigen-recognition domains and T-cell signalling domains. T-cells genetically engineered to express CARs can specifically recognise antigens. Success of CAR-T cells against leukaemia and lymphoma has encouraged the development of CAR-T therapies for MM. BCMA is expressed by normal and malignant plasma cells. CAR-Ts targeting BCMA have demonstrated significant anti-myeloma activity in early clinical trials. Toxicities in these trials, including cytokine release syndrome, have been similar to toxicities observed in CAR-T trials for leukaemia.[4] CAR-T cell therapy combines the advantage of target specificity of monoclonal antibodies and cytotoxicity of T-cells.[5]

Ciltacabtagene autoleucel is an anti-BCMA CAR-T cell therapy. Another CAR-T, idecabtagene vicleucel, received conditional marketing authorisation from EMA for MM in Aug 2021.[6,7]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

This product is not licensed for any indication in the EU/UK.

Ciltacabtagene autoleucel has been granted the following designations:[8,9]

- Orphan Drug designation by the European Medicines Agency (EMA) (EU/3/20/2252) in February 2020
- Breakthrough Therapy designation in December 2019 by the US Food and Drug Administration (FDA)
- Orphan Drug designation by the FDA in February 2019.

In March 2019, ciltacabtagene autoleucel was given PRIME designation by the EMA, the designation is "under evaluation" as of July 2021.[10,11]

PATIENT GROUP

DISEASE BACKGROUND

MM is a type of bone marrow cancer that is characterised by uncontrolled proliferation of monoclonal plasma cells in the bone marrow, resulting in the over-production of monoclonal immunoglobulin, and immunosuppression, as well as osteolysis and end-organ damage.[12,13] MM can affect several bones in the body such as the spine, skull, pelvis and ribs, as well as the blood, kidney and immune system.[12,14] In the early stages, MM does not cause any symptoms and is often diagnosed after a routine blood or urine test. In later stages, MM causes symptoms including: a persistent dull ache or areas of tenderness in your bones, weak bones that fracture easily, tiredness, weakness, shortness of breath, anaemia, repeated infections, kidney problems, bruising and unusual bleeding (for example frequent nose bleeds, bleeding gums and heavy periods).[12]

The exact cause of MM is not known; however, it is associated with monoclonal gammopathy of unknown significance (MGUS) which causes an excess of immunoglobins in the blood. Risk factors for MM include age, gender and ethnicity. The risk of MM increases with age, with most people diagnosed in their mid-60s. Men are more likely to develop the disease than women, and MM is twice as common in black compared with white populations. Having a family history of the disease is another risk factor for MM.[12,15]

When diagnosed, MM is staged using the international staging system (ISS) which is based on two blood tests. These tests measure the amount of β2-microglobulin (β2-M), albumin and lactate dehydrogenase (LDH) in the blood. MM is then classified further by levels of calcium and kidney damage markers, anaemia and bone damage, as well as whether the patient is symptomatic or asymptomatic.[16]

Although the survival rates for MM have increased, it still remains a condition that is incurable and features a high relapse rate.[17] Relapsed (or recurrent) MM is when cancer returns after treatment or after a period of remission.[16] Refractory MM is defined as disease that is nonresponsive while on primary or salvage therapy, or progresses within 60 days of the previous therapy.[18]

CLINICAL NEED AND BURDEN OF DISEASE

In 2016, MM was the 19th most common cancer in the UK, accounting for 2% of all new cancer cases.[19] In England, in 2017, there were 5,034 newly diagnosed cases of MM and malignant plasma cell neoplasms (ICD-10: C90). Incidence is strongly linked to age, with the highest rates

in people ages 70 to 89 years.[20] Over the last decade, incidence rates have increased by a seventh (to 15%), represented by an increase in males by 15% and in females by 12%. Incidence rates are projected to rise by 11% in the UK between 2014 and 2035 to 12 cases per 100,000 by 2035.[19] A systematic review and economic evaluation carried out in Europe in 2015 found that almost 10% of patients treated were relapsed or refractory to both proteasome inhibitors and immunomodulatory agent based treatment regimens.[21]

In England, in 2019-20, there were 159,091 finished consultant episodes and 153,239 hospital admissions with a primary diagnosis of MM and malignant plasma cell neoplasms (ICD-10 code: C90.0), resulting in 101,411 bed days and 137,398 day cases.[22] Almost half (52.3%) of people diagnosed with MM in England and Wales survive their disease for 5 years or more, with a third surviving for 10 years or more.[19] In England and Wales in 2020, there were 2,881 registrations of death where MM was recorded as the underlying cause.[23]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

Most patients experience serial relapse and will be treated with most available agents at some point during their disease course.[24] The choice of therapy in the relapsed setting depends on several parameters such as age, performance status, comorbidities, the type, efficacy and tolerance of the previous treatment, the number of prior treatment lines, the available remaining treatment options, the interval since the last therapy and the type of relapse (i.e. clinical versus biochemical relapse; in the case of biochemical relapse, treatment can be delayed).[25] The length of the prior remission duration is a critical component in making a choice of salvage therapy. The depth of the first response, remission duration of the patient's prior therapies, and tumour burden at relapse can suggest the aggressiveness of the relapse.[26]

A non-pharmacological treatment option for relapsed or refractory MM is a second autologous stem cell transplant, depending on the response to the first.[27] Patients may also receive medicines and procedures to prevent and treat problems caused by MM rather than the condition itself– such as bone pain, fractures and anaemia.[12]

CURRENT TREATMENT OPTIONS

NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:[27]
In instances of first relapse, the guidelines recommend the use of:

- Daratumumab plus bortezomib plus dexamethasone.
- Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib.
- Bortezomib monotherapy – only after one prior therapy and for adults who have undergone, or are unsuitable for, bone marrow transplantation.

Subsequent relapse treatment may include:[27]

- Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent.
- Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse; that is, after three previous treatments including both lenalidomide and bortezomib.

- Daratumumab monotherapy for adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.
- Isatuximab with pomalidomide and dexamethasone for treating relapsed and refractory MM patients after 3 previous therapies

PLACE OF TECHNOLOGY

If licensed, ciltacabtagene autoleucel will provide an additional treatment option for adults with relapsed and lenalidomide-refractory MM.

CLINICAL TRIAL INFORMATION

Trial	**CARTITUDE-4;** NCT04181827; 2019-001413-16; A Phase 3 Randomised Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against BCMA, Versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects With Relapsed and Lenalidomide-Refractory Multiple Myeloma **Phase III** - Recruiting **Location(s):** 11 EU countries, UK, USA and other countries **Primary completion date:** April 2026
Trial design	Randomised, parallel assignment and open label
Population	N = 400, multiple myeloma; have received 1 to 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD); Refractory to lenalidomide per International Myeloma Working Group (IMWG) consensus guidelines; aged 18 years and older
Intervention(s)	Arm B: Participants will receive bridging therapy (PVd or DPd), conditioning regimen (cyclophosphamide and fludarabine, IV) and JNJ-68284528 (IV)
Comparator(s)	Arm A: Participants will receive either PVd or DPd as a standard therapy.
Outcome(s)	Primary outcome; • Progression Free Survival (PFS) [Time Frame: Until end of the study (up to 6 years)] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

The cost of ciltacabtagene autoleucel is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Carfilzomib with daratumumab and dexamethasone for treating relapsed or refractory multiple myeloma (ID2709). Expected date of issue: October 2022.
- NICE technology appraisal in development. Melphalan flufenamide with dexamethasone for treating relapsed or refractory multiple myeloma (ID3862). Expected date of issue: June 2022
- NICE technology appraisal in development. Isatuximab with pomalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA658). Expected date of issue: November 2020.
- NICE technology appraisal. Lenalidomide plus dexamethasone for multiple myeloma after 1 treatment with bortezomib (TA586). June 2019.
- NICE technology appraisal. Lenalidomide for the treatment of multiple myeloma in people who have received at least 2 prior therapies (TA171). June 2019.
- NICE technology appraisal. Daratumumab with bortezomib and dexamethasone for previously treated multiple myeloma (TA573). April 2019
- NICE technology appraisal. Daratumumab monotherapy for treating relapsed and refractory multiple myeloma (TA510). March 2018.
- NICE technology appraisal. Ixazomib with lenalidomide and dexamethasone for treating relapsed or refractory multiple myeloma (TA505). February 2018.
- NICE technology appraisal. Carfilzomib for previously treated multiple myeloma (TA457). July 2017.
- NICE technology appraisal. Pomalidomide for multiple myeloma previously treated with lenalidomide and bortezomib (TA427). January 2017.
- NICE technology appraisal. Panobinostat for treating multiple myeloma after at least 2 previous treatments (TA380). January 2016.
- NICE technology appraisal. Bortezomib monotherapy for relapsed multiple myeloma (TA129). October 2007.
- NICE guideline. Myeloma: diagnosis and management (NG35). October 2018.
- NICE guideline. Haematological cancers: improving outcomes (NG47). May 2016.
- NICE quality standard. Haematological cancers (QS150). June 2017.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. Clinical Commissioning Policy: Second allogeneic haematopoietic stem cell transplant for relapsed disease (all ages). 2017. 16068/P
- NHS England. Clinical Commissioning Policy: Haematopoietic Stem Cell Transplantation (HSCT)(All Ages): Revised. 2015. B04/P/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.
- NHS England. 2013/14. NHS Standard Contract for Haematopoietic Stem Cell Transplantation (Adult). B04/S/a.

OTHER GUIDANCE

- European Myeloma Network perspective on CAR T-Cell therapies for multiple myeloma. 2021.[28]
- NCCN Guidelines Insights: Multiple Myeloma, Version 3. 2018.[29]
- NHS England. NHS manual for prescribed specialist services. Chapter 29: blood and marrow transplantation services (adults and children). 2018/2019.[30]
- The UK Myeloma Forum (UKMF) and the British Society for Haematology (BSH). Guidelines for screening and management of late and long-term consequences of myeloma and its treatment. 2017.[31]
- ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up: Multiple myeloma. 2017.[31]
- NHS England. National chemotherapy algorithms - multiple myeloma. 2015.
- The International Myeloma Working Group. Revised International Staging System for Multiple Myeloma: A Report from IMWG. 2015. [32]
- The Haemato-oncology Task Force of the British Committee for Standards in Haematology (BCSH) and UK Myeloma Forum. Guidelines for the diagnosis and management of Multiple Myeloma. 2014.[33]

ADDITIONAL INFORMATION

REFERENCES

1 Clinicaltrials.gov. A Phase 3 Randomized Study Comparing JNJ-68284528, a Chimeric Antigen Receptor T Cell (CAR-T) Therapy Directed Against BCMA, Versus Pomalidomide, Bortezomib and Dexamethasone (PVd) or Daratumumab, Pomalidomide and Dexamethasone (DPd) in Subjects With Relapsed and Lenalidomide-Refractory Multiple Myeloma. *Trial ID: NCT04181827*. 2019;Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04181827.

2 National Cancer Institute. *autologous bi-epitope BCMA-targeted CAR T cells JNJ-68284528.* Available from: https://www.cancer.gov/publications/dictionaries/cancer-drug/def/792630 [Accessed 10 August 2021].

3 Janssen Research & Development. *Janssen Presents Initial Results for BCMA CAR-T Therapy JNJ-4528 Showing Early, Deep and High Responses in the Treatment of Relapsed or Refractory Multiple Myeloma.* 2019. Available from: https://www.jnj.com/janssen-presents-initial-results-for-bcma-car-t-therapy-jnj-4528-showing-early-deep-and-high-responses-in-the-treatment-of-relapsed-or-refractory-multiple-myeloma [Accessed 10 August 2021].

4 Mikkilineni L, Kochenderfer J. Chimeric antigen receptor T-cell therapies for multiple myeloma. *Blood*. 2017;130(24):2594-602. Available from: https://doi.org/10.1182/blood-2017-06-793869.

5 Yu B, Jiang T, Liu D. BCMA-targeted immunotherapy for multiple myeloma. *Journal of Hematology & Oncology*. 2020;13:125. Available from: https://doi.org/10.1186/s13045-020-00962-7.

6 National Insititute for Health and Care Excellence (NICE). *Managing myeloma.* 2020. Available from: https://pathways.nice.org.uk/pathways/myeloma#path=view%3A/pathways/myeloma/managing-myeloma.xml [Accessed 10 August 2021].

7 European Medicines Agency. *First cell-based gene therapy to treat adult patients with multiple myeloma.* 2021. Available from: https://www.ema.europa.eu/en/news/first-cell-based-gene-therapy-treat-adult-patients-multiple-myeloma [Accessed 10 August 2021].

8 Johnson and Johnson. *Janssen Announces BCMA CAR-T Therapy JNJ-4528 Granted U.S. FDA Breakthrough Therapy Designation for the Treatment of Relapsed or Refractory Multiple Myeloma.* Available from: https://www.jnj.com/janssen-announces-bcma-car-t-therapy-jnj-4528-granted-u-s-fda-breakthrough-therapy-designation-for-the-treatment-of-relapsed-or-refractory-multiple-myeloma [Accessed 10 August 2021].

9 European Commission. *Community Register of orphan medicinal products,*. Available from: https://ec.europa.eu/health/documents/community-register/html/o2252.htm [Accessed 10 August 2021].

10 European Medicines Agency. *PRIME: priority medicines.* 2021. Available from: https://www.ema.europa.eu/en/human-regulatory/research-development/prime-priority-medicines [Accessed 10 August 2021].

11 Johnson and Johnson. *Janssen Announces Investigational CAR-T Therapy JNJ-68284528 Granted PRIME Designation by the European Medicines Agency.* Available from: https://www.jnj.com/janssen-announces-investigational-car-t-therapy-jnj-68284528-granted-prime-designation-by-the-european-medicines-agency [Accessed 10 August 2021].

12 National Health Service. *Overview: Multiple myeloma.* Available from: https://www.nhs.uk/conditions/multiple-myeloma/ [Accessed 10 August 2021].

13 Hipp S, Tai Y-T, Blanset D, Deegen P, Wahl J, THomas O, et al. A novel BCMA/CD3 bispecific T-cell engager for the treatment of multiple myeloma induces selective lysis in vitro and in vivo. *Leukemia*. 2017;31(8):1743-51. Available from: https://doi.org/10.1038/leu.2016.388.

14 National Institute for Health Care Excellence (NICE). *Multiple Myeloma.* 2016. Available from: https://cks.nice.org.uk/multiple-myeloma#!backgroundSub [Accessed 10 August 2021].

15 Cancer Research UK. *Myeloma - Risks and causes.* Available from: https://www.cancerresearchuk.org/about-cancer/myeloma/risks-causes [Accessed 10 August 2021].

16 Cancer Research UK. *Stages of myeloma.* 2020. Available from: https://www.cancerresearchuk.org/about-cancer/myeloma/stages [Accessed 10 August 2021].

17 Sonneveld P, Broiji A. Treatment Of Relapsed And Refractory Multiple Myeloma. *Haematologica*. 2016;101:396-406. Available from: https://doi.org/10.3324/haematol.2015.129189.

18 Rajkumar S, Harousseau J, Durie B, Anderson K, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117(18):4691-5. Available from: https://doi.org/10.1182/blood-2010-10-299487.

19 Cancer Research UK. *Myeloma statstics.* 2017. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/myeloma#heading-Zero [Accessed 11 August 2021].

20 Office for National Statistics (ONS). *Cancer registration statistics, England*. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Downloaded 26 April 2021].

21 Gatopoulou X, Bardenheuer K, Van Hoorenbeeck S, Kempel A. Treatment Patterns of Relapsed and Refractory Multiple Myeloma in Europe (EU-28). *Value in Health*. 2016:A715-6. Available from: https://www.valueinhealthjournal.com/article/S1098-3015(16)33480-5/pdf.

22 National Health Service. *Hospital Admitted Patient Care Activity 2019-20.* Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20 [Accessed 11 August 2021].

23 Office for National Statistics. *Deaths registered in England and Wales – 21st century mortality.* 2021. Available from: https://www.ons.gov.uk/file?uri=%2fpeoplepopulationandcommunity%2fbirthsdeathsandmarriages%2fdeaths%2fdatasets%2fthe21stcenturymortalityfilesdeathsdataset%2fcurrent/21stcenturymortality2020.xls [Accessed 11 August 2021].

24 Uptodate. *Multiple Myeloma: Treatment of relapse or refractory disease.* Available from: https://www.uptodate.com/contents/multiple-myeloma-treatment-of-relapsed-or-refractory-disease?search=multiple-myeloma-treatment-of-relapsed-orrefractorydisease&source=search_result&selectedTitle=2~150&usage_type=default&display_rank=2 [Accessed 11 August 2021].

25 Moreau O, San Miguel J, Sonneveld P, Mateos M, Zamagni E, Avet-Loiseau H, et al. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2017;28(4):52-61. Available from: https://doi.org/10.1093/annonc/mdx096.

26 Nooka A, Kastritis E, Dimopoulos M, Lonial S. Treatment options for relapsed and refractory multiple myeloma. *Blood*. 2015;125(20):3085-99. Available from: https://doi.org/10.1182/blood-2014-11-568923.

27 National Institute for Health Care Excellence. *Managing relapse of myeloma* Last Update Date: Available from: http://pathways.nice.org.uk/pathways/myeloma [Accessed 11 August 2021].

28 Bruno B, Wäsch R, Engelhardt M, Gay F, Giaccone L, D'Agostino M, et al. European Myeloma Network perspective on CAR T-Cell therapies for multiple myeloma. *Haematologica*. 2021 04/01;106(8):2054-65. Available from: https://doi.org/10.3324/haematol.2020.276402.
29 Kumar S, Callander N, Alsina M, Atanackovic D, Biermann J, Castillo J, et al. NCCN Guidelines Insights: Multiple Myeloma, Version 3.2018. *Journal of the National Comprehensive Cancer Network*. 2018;16(1):11-20. Available from: https://jnccn.org/view/journals/jnccn/16/1/article-p11.xml.
30 NHS England. *Manual for Prescribed Specialised Services 2018/19.* 2018/19. Available from: https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual.pdf [Accessed 11 August 2021].
31 European Society Medical Oncology. Multiple Myeloma: ESMO Clinical Practice Guidelines. *Annals of Oncology*. 2017;28:52-61. Available from: https://www.esmo.org/guidelines/haematological-malignancies/multiple-myeloma.
32 Palumbo A, Avet-Loiseau H, Oliva S, Lokhorst H, Goldschmidt H, Rosinol L, et al. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *Journal of Clinical Oncology*. 2015;33(6):2865-9. Available from: https://doi.org/10.1200/JCO.2015.61.2267.
33 Bird J, Owen R, D'Sa S, Snowden J, Pratt G, Ashcroft J, et al. Guidelines for the diagnosis and management of multiple myeloma 2011. *British journal of haematology*. 2011;154(1):32-75. Available from: https://doi.org/10.1111/j.1365-2141.2011.08573.x.

NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.