Institution: University of Leeds

Unit of Assessment: 1

Title of case study: The only RCT evidence on salvage autologous stem cell transplantation (sASCT) in relapse myeloma leads to worldwide guidelines and increased sASCT uptake

Period when the underpinning research was undertaken: 2005-2020

Details of staff conducting the underpinning research from the submitting unit:

Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Gordon Cook	Clinical Professor Haematology	2013-present
Julia Brown	Professor of Clinical Trials	1991-present
David Cairns	Senior Research Fellow in Biostatistics;	2009-2013;
	Associate Professor of Statistics in Late Phase Cancer Clinical Trials	2013-present

Period when the claimed impact occurred: 2013-2020

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

Our researchers designed the National Cancer Research Institute approved Myeloma X trial. Myeloma X provided the first and only global 'real-world' clinical data for the benefits of Salvage autologous stem cell transplantation (sASCT) for relapse multiple myeloma. Previously, sASCT was clinically available, but not evidenced by prospective clinical trials or real-world data. Following Myeloma X, sASCT was adopted in national and international guidelines, accepted for reimbursement, and resulted in a change in clinical practice (indexed through a measured increased uptake into routine standard care practice).

2. Underpinning research (indicative maximum 500 words)

The use of high dose chemotherapy and autologous stem cell transplantation (ASCT) is standard first-line therapy for multiple myeloma (MM). However, the management of relapsed MM following typical first-line ASCT evolved without randomised controlled trial evidence of clinical effectiveness. In the relapse setting, salvage ASCT (sASCT) was utilised in some areas of clinical practice based on evidence from retrospective registry or single centre studies only, primarily without the incorporation of novel agents in the re-induction phase. Thus, the application of sASCT in the modern clinical era lacked an acceptable evidence base.

Leeds researchers first conducted a retrospective case-matched control analysis on 106 patients who underwent sASCT compared with conventional chemotherapy, and found improved overall survival and progression-free survival compared with conventional chemotherapy [**1**]. However, there was a clear unmet need to define the utility of sASCT in the era of novel agents. This required prospective, randomised, multi-centre data that could evidence the clinical effectiveness and quality of life impact.

To address this clinical uncertainty, researchers at the University of Leeds (G. Cook, D. Cairns, J. Brown) designed and initiated the NCRI-badged UK Myeloma Forum Myeloma X study, funded by Cancer Research UK. This multi-centre, phase III study investigated non-transplant strategy in patients in relapse after a standard first-line ASCT, and compared the effectiveness of sASCT

versus a common modern-day re-induction regimen (bortezomib, adriamycin and dexamethasone - known as PAD). The primary outcome was time to disease progression, and secondary outcomes included overall survival and quality of life [**2**]. Additionally, the study explored whether stem cells could be harvested after a prior ASCT (otherwise the adoption of sASCT would be limited), and investigated molecular risk factors in first relapse.

Across 51 UK centres, 297 first relapse patients were registered, of whom 293 received PAD re-induction therapy. Following this, 174 patients had sufficient peripheral blood stem cell mobilisation to continue treatment, of which 89 were randomised to sASCT and 85 to cyclophosphamide. After a median follow-up of 31 months, the trial demonstrated improvement in time to disease progression in the sASCT group of 19 months, compared to 11 months in the cyclophosphamide group [**2**]. Long-term follow-up demonstrated that median overall survival was superior in sASCT compared to cyclophosphamide (67 months vs 52 months) [**3**].

For the first time, there was a comprehensive analysis of molecular risk makers in first relapse, and data on how these impacted the results of the Myeloma X trial [**4**]. Interphase fluorescence *in situ* hybridization (I-FISH) was used to investigate genetic abnormalities. The majority of high-risk markers, when considered individually, were not shown to prevent progression-free survival and overall survival of sASCT compared with weekly cyclophosphamide. However, there was evidence of a detrimental impact from MYC gene rearrangement - a well-known marker of poor prognosis. Current clinical interventions do not circumvent this adversity, highlighting the need for newer targeted strategies for this sub–group of patients.

From a practical, real-world delivery perspective, these trial outcomes were supported by the ability to mobilise and harvest stem cells at first relapse, an important logistical issue without which uptake in clinical practice would be limited [**5**]. The study demonstrated that the advantages demonstrated by sASCT in terms of durability of disease control and survivorship did not compromise quality of life [**6**].

3. References to the research (indicative maximum of six references)

1. **G Cook**, E Liakopoulou, GJ Morgan, FE Davies, R Pearce, C Williams, K Towlson, E Morris, J Cavet, TCM Morris, NH Russell & DI Marks. (2011) Factors influencing the outcome of second autologous transplant in relapsed multiple myeloma: A study from the British Society of Blood and Marrow Transplantation Registry. Biology of Blood & Marrow Transplantation, 17(11):1638-45. DOI: 10.1016/j.bbmt.2011.04.005

2. **G Cook**, C Williams, **JM Brown**, **DA Cairns**, J Cavenagh, JA Snowden, AJ Ashcroft, M Fletcher, C Parrish, K Yong, J Cavet, H Hunter, JM Bird, A Chalmers, S O'Connor, MT Drayson & TCM Morris On behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. (2014) High-dose chemotherapy plus autologous stem-cell transplantation as consolidation therapy in patients with relapsed multiple myeloma after previous autologous stem-cell transplantation (NCRI Myeloma X Relapse [Intensive trial]): a randomised, open-label, phase 3 trial. The Lancet Oncology, 15(8):874-85. DOI: 10.1016/S1470-2045(14)70245-1

3. **G Cook**, AJ Ashcroft, **DA Cairns**, C Williams, A Hockaday, JD Cavenagh, JA Snowden, C Parrish, K Yong, J Cavet, H Hunter, JM Bird, G Pratt, S Chown, E Heartin, S O'Connor, MT Drayson, **JM Brown** & TCM Morris on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. (2016) A salvage autologous stem cell transplant (sASCT) induces superior overall survival following Bortezomib-containing re-induction therapy for relapsed multiple myeloma (MM): Results from the Myeloma X (Intensive) Trial. The Lancet Haematology, 3(7):e340–e351. DOI: 10.1016/S2352-3026(16)30049-7

4. **G Cook**, KL Royle, **JM Brown**, AJ Ashcroft, CD Williams, A Hockaday, JD Cavenagh, JA Snowden, D Ademokun, E Tholouli , V Andrews, M Jenner, C Parrish, K Yong, J Cavet, H Hunter, JM Bird, G Pratt, S O'Connor, MT Drayson, DA **Cairns** & TCM Morris, on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. (2019) The impact of

cytogenetics on response and overall survival in patients with relapsed multiple myeloma (long-term follow-up results from BSBMT/UKMF Myeloma X Relapse [Intensive]): a randomised, open-label, phase 3 trial. British Journal of Haematology, 185(3):50-67. DOI: 10.1111/bjh.15782

5. C Parrish, TCM Morris, C Williams, **DA Cairns**, J Cavenagh, JA Snowden, AJ Ashcroft, J Cavet, H Hunter, JM Bird, A Chalmers, **J Brown**, K Yong, S Schey, S Chown & **G Cook** on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. (2016) Stem cell harvesting after re-induction with a Bortezomib-based regimen for multiple myeloma relapsing after autologous stem cell transplant is feasible, safe and effective: Results from the BSBMT/UKMF Myeloma X (Intensive) Trial. Biol Bone Marrow Transplantation, 22(6):1009-1016. DOI: 10.1016/j.bbmt.2016.01.016

6. SH Ahmedzai, JA Snowden, AJ Ashcroft, **DA Cairns**, C Williams, A Hockaday, JD Cavenagh, D Ademokun, E Tholouli, D Allotey, V Dhanapal, M Jenner, K Yong, J Cavet, H Hunter, JM Bird, G Pratt, C Parrish, JM Brown, TCM Morris & **G Cook** on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. (2019) Patient-reported outcome results from the open-label, randomized Phase III Myeloma X Trial evaluating salvage autologous stem-cell transplantation in relapsed multiple myeloma. Journal of Clinical Oncology, 37(19):1617-1628. DOI: 10.1200/JCO.18.01006

4. Details of the impact (indicative maximum 750 words)

Worldwide incidence of MM is currently 160,000, and mortality is 106,000. In the UK, there are around 5,800 new myeloma cases every year, with incidence rates projected to rise by 11% between 2014 and 2035, to 12 cases per 100,000 people. The introduction of ASCT to support high-dose melphalan in patients with MM in the 1980s represented a step change in the management of this disease, with randomised trials confirming its clinical use to be better than conventional chemotherapy in terms of progression-free and overall survival. Consequently, the procedure is regarded as standard care for the treatment of patients with newly diagnosed MM up to the age of 65–70 years without significant comorbidities. The incorporation of novel drugs (thalidomide, bortezomib, and lenalidomide) into the first-line management strategy during induction, consolidation, or maintenance in the past 15 years has further contributed to improving patient outcomes. However, for the vast majority of patients, cure remains elusive and the disease will eventually relapse.

The NCRI-badged UK Myeloma Forum Myeloma X trial, designed and delivered by Leeds researchers (Cook, Brown and Cairns) is the only global, prospective interventional study in this setting, and demonstrated a superior durability of response (time to progression and progression-free survival) when sASCT is used compared to non-transplant consolidation [**2**,**3**].

Furthermore, Myeloma X showed the durability of response is maintained in the subsequent line of therapy (time to second objective disease progression), and demonstrated a superior survivorship advantage [**3**]. This provides the first, and only, randomised evidence to suggest a survivorship benefit for sASCT [**A**], with no significant influence being inferred by β2-microglobulin at relapse and age, though adverse molecular markers continue to show poorer response [**4**]. Myeloma X demonstrated that this survivorship advantage is not at the expense of quality of life measurements [**6**].

Inclusion in national guidelines increases uptake and improves patient outcomes
The trial output has delivered the necessary prospective evidence in an up-to-date clinical treatment scenario to demonstrate the clinical effectiveness of sASCT in first relapsed MM. Consequentially, the study has informed the recommendations of national guidelines in the UK. A sASCT is considered 'standard' by the British Society of Blood and Marrow Transplantation (BSBMTCT) Indications Committee [**B**], and has been approved and recommended by the National Institute for Health and Care Excellence [**C**].

Updates to the UK Myeloma Forum guidelines on the diagnosis and management of multiple

myeloma, produced on behalf of the British Committee for Standards in Haematology in 2014, reflected our trial outcomes on the clinical utility of sASCT, with Cook a contributing author for both the original guideline and amendment [**D**].

This has resulted in MM being the first disease group to have the baseline commissioning policy approval for sASCT in first relapse by NHS England (and devolved governments). This, in turn, has led to a change in clinical practice, with recorded increase in the number of patients undergoing sASCT in the UK (from 160 per annum in 2012 to 293 per annum in 2019) [**E**].

The MM care pathway is multi-faceted, and continually evolving, but sASCT is a recognised clinical utility. The survivorship of patients is the culmination of all treatment lines but Myeloma X has shown that use of sASCT has a positive impact on survivorship. Real-world outcomes in 50-69 year olds eligible for sASCT, show a 2.3% point improvement in the 50-59 age group at 5 years from diagnosis, and a 4% improvement in the 60-69 age group [**F**]. This is the effect of several evolutions in clinical care but includes the impact of sASCT, and is not related to the impact of the (very) recently adopted monoclonal antibody therapy (daratumumab).

Sole global data on sASCT for relapse MM leads to adoption in international guidelines
The Myeloma X trial results have been pivotal to formulating the recommendations for international guidelines. The International Myeloma Working Group (IMWG) emerged through the International Myeloma Foundation in order to promote collaborative research, and reach consensus for guidelines. Together with the Blood and Marrow Transplant Clinical Trials Network, the American Society of Blood and Marrow Transplantation, and the European Society of Blood and Marrow Transplantation (ESBMT), IMWG produced guidelines that included our recommendations [**G**].

The Deputy Division Head of Hematologic Malignancies, Memorial Sloan Kettering Cancer Center, New York, who co-led the guidelines, said:

*"Dr Cook and his colleagues from Leeds University have been instrumental not only in filling the knowledge gap, but in encouraging others to study this important and potentially more cost-effective strategy for remission consolidation in patients with myeloma failing primary therapy [**H**]."*

These guidelines have led to increased uptake of sASCT into routine clinical practice as a standard of care in the United States since 2015, with the Leeds research having a:

"direct impact on the improved survival of multiple myeloma patients" [**I**].

It is estimated that 100 patients a year in the US have benefitted from this treatment [**H**]. Similar benefits have been reported in France and other European countries [**J**].

Our trial results have also been adopted in the American Society of Clinical Oncology and Cancer Care Ontario joint clinical practice guideline on the treatment of MM [**K**], and incorporated into a ESBMT report addressing the issue of myeloma treatment relapse options following a previous autologous transplantation, where it recognised the Leeds research as:

*"offering a dataset on which to base clinical decision making [**L**]."*

The consequence of this research is shown through real-world evidence demonstrating increased uptake of sASCT into routine practice as a standard of care as a consequence of presenting and publishing the results (BSBMT and ESBMT registries). Taken together, the results of this study are already having an impact on the clinical management pathway in myeloma and helping the decision-making process for both physicians and myeloma patients.

5. Sources to corroborate the impact (indicative maximum of 10 references)

A. R Al Hamed, AH Bazarbachi, F Malard, J-L Harousseau & M Mohty. (2019) Current status of autologous stem cell transplantation for multiple myeloma. Blood Cancer Journal, 9(44). DOI:

10.1038/s41408-019-0205-9

B. BSBMTCT. (2013) BSBMTCT Indications for Adult BMT (Oct 2013). https://bsbmtct.org/indications-table/
Used by NHS England to reimburse therapy

C. NICE. (2018) Myeloma: diagnosis and management. NG35: 271-287. NICE, London. https://www.nice.org.uk/guidance/ng35

D. Pratt G, Jenner M, Owen R, Snowden JA, Ashcroft J, Yong K, Feyler S, Morgan G, Cavenagh J, Cook G, Low E, Stern S, Behrens J, Davies F, Bird J. (2014) Updates to the guidelines for the diagnosis and management of multiple myeloma. British Journal of Haematology, 167(1):131-3. DOI: 10.1111/bjh.12926

E. BSBMTCT data on real-world use, including sASCT, from 2012-2019

F. Office for National Statistics. (2016) Real-world outcomes at 5- and 1-year from diagnosis pre- and post-Myeloma X trial. https://tinyurl.com/53gecnsv

G. S Giralt, L Garderet, B Durie, G Cook, et al (2015) American Society of Blood and Marrow Transplant, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in Patients with Relapsed Multiple Myeloma. Biology of Blood and Marrow Transplantation, 21(12):2039-51. DOI: 10.1016/j.bbmt.2015.09.016.

H. Testimonial letter from the Deputy Division Head of Hematologic Malignancies, Memorial Sloan Kettering Cancer Center, New York

I. Testimonial letter from the Director of the Transplant and Cellular Therapy Program, Roswell Park Comprehensive Cancer Center and Internal Medicine, SUNY at Buffalo

J. Testimonial letter from the Chair of the European Blood and Marrow Transplant Society (EBMT)

K. J Mikhael, N Ismaila, MC Cheung, C Costello, MV Dhodapkar, S Kumar, M Lacy, B Lipe, RF Little, A Nikonova, J Omel, N Peswani, A Prica, N Raje, R Seth, DH Vesole, I Walker, A Whitley, TM Wildes, SW Wong & T Martin. (2019) Treatment of Multiple Myeloma: ASCO and CCO Joint Clinical Practice Guideline. Journal of Clinical Oncology, 37(14):1228-1263. DOI: 10.1200/JCO.18.02096

L. L Garderet, G Cook, H Auner, B Bruno, H Lokhorst, JA Perez, F Sahebi, C Scheid, C Morris, G Gahrton, S Schoenland, N Kroger. (2016) Treatment options for relapse after autograft in multiple myeloma (consensus report from an EBMT educational meeting). Leukaemia & Lymphoma, 58(4):797-808. DOI: 10.1080/10428194.2016.1228926.