Institution: University of Sheffield		
Unit of Assessment: A-01 Clinical Medicine		
Title of case study: Autologous haematopoietic stem cell treatment: A novel disease-modifying treatment for relapsing-remitting multiple sclerosis		
Period when the underpinning research was undertaken: 2011-2019		
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:**
John Snowden	Honorary Professor of Haemato-oncology & Stem Cell Transplantation	2002-2018
Basil Sharrack	Honorary Professor of Clinical Neurology	2011-present
Period when the claimed impact occurred: 2012-present		
Is this case study continued from a case study submitted in 2014? N		

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

The Sheffield team pioneered autologous haematopoietic stem cell treatment (AHSCT) as a novel treatment in relapsing-remitting multiple sclerosis (RRMS) and headed the UK arm of the first international phase II randomized controlled trial that compared AHSCT with other disease-modifying treatments (DMTs). This trial showed that AHSCT halted disease progression and improved disability outcomes. AHSCT has since been incorporated into national and international guidelines and clinical practice as the “standard of care” with direct benefits to patient quality of life and ever-increasing cost savings. The ongoing impact has been nationally recognized in the 2019 National Future NHS Parliamentary and the 2020 Queen Anniversary Awards, and internationally by the 2020 Clinical Research Forum (USA) Top Ten Research Achievement Award.

2. Underpinning research (indicative maximum 500 words)

Multiple sclerosis (MS) is a chronic immune-mediated inflammatory disease of the central nervous system. In 2016, there were 2,221,188 prevalent cases of multiple sclerosis globally. In the UK, there are currently ~130,000 MS patients, and 6,700 people are diagnosed with MS each year. The US currently has ~1 million MS cases. RRMS is the most common form of MS, affecting about 85% of people diagnosed with MS. A challenge in the treatment of MS has been that DMTs reduced relapse rate and slowed the accumulation of disability to varying degrees, but they did not halt its progression.

To address the limitations of the available DMTs, research by Professors Snowden and Sharrack investigated the treatment of RRMS with AHSCT, is a novel therapeutic strategy based on purging autoreactive lymphocytes with the use of chemotherapy-based ‘conditioning regimens’ and restarting the immune system using the patient’s own haematopoietic stem cells in a new non-inflammatory environment. Snowden has pioneered the use of AHSCT in various autoimmune disorders (ADs). In 2011, Snowden performed the first national analysis of long-term outcomes of HSCT in ADs based on the British Society of Blood and Marrow (BSDM) Transplantation Data Registry. This study concluded that the treatment of poor-risk but reversible ADs in patients with adequate fitness for HSCT is warranted [R1]. Sharrack has been at the forefront of the development of AHSCT as a novel disease-modifying therapy for RRMS. In 2015, with co-researchers from Northwest University, he published the results of an

uncontrolled trial showing that among patients with RRMS, AHSCT was associated with significant improvement in neurological disability [R2].

As members of the MS-AHSCT Long-Term Outcomes Study Group, Snowden and Sharrack contributed to an observational study of long-term disability outcomes of patients with RRMS. The results showed that nearly half of these patients were free of neurological progression 5 years after receiving AHSCT [R3].

Following these uncontrolled trials, Sharrack and Snowden led the UK arm of the first international phase II randomized controlled trial (conducted in four sites—Chicago (US), Sheffield (UK), Uppsala (Sweden) and Sao Paulo (Brazil)) that compared AHSCT with other DMTs (MIST Study; ClinicalTrials.gov Identifier: NCT00273364). The trial showed that in patients with RRMS, compared with standard DMTs, AHSCT halted disease progression in the majority of patients who received it. Notably, there was significant improvement in the level of disability in patients treated with AHSCT. In particular, there was no evidence of disease activity (i.e., no evidence of relapses, disability progression or MRI disease activity) in 68%–70% of the AHSCT patients at 5 years following the transplant (see figure). In contrast, less than 8% of patients treated with various DMTs achieved 'no evidence of disease activity' status. Furthermore, the majority of patients in whom standard DMTs failed during the course of trial significantly improved when they crossed over to receive AHSCT, challenging the traditional dogma that disability progression in MS is irreversible [R4]. Overall, the MIST trial showed that AHSCT is the most effective treatment in patients with active RRMS [R4, Figure 1].

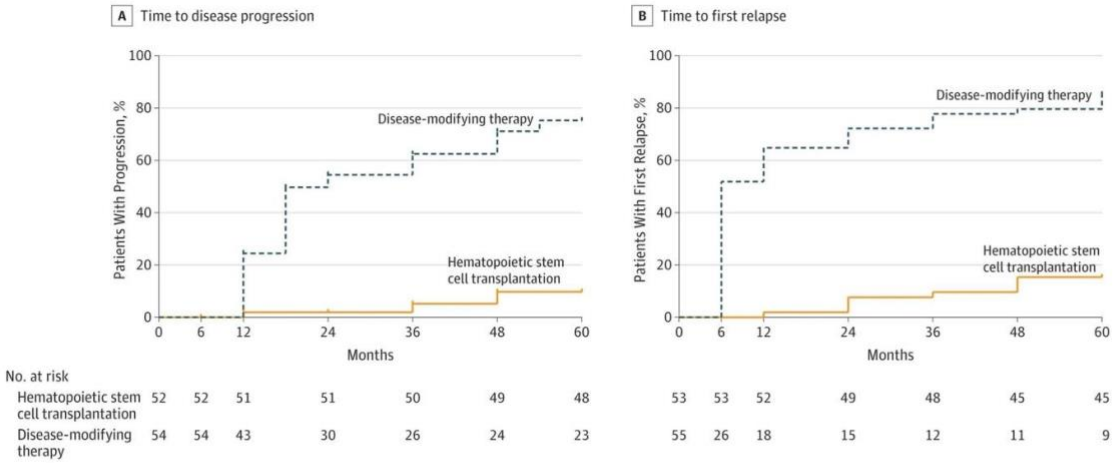

Figure legend – Time to Disease Progression and First Relapse Among Patients Receiving Hematopoietic Stem Cell Transplantation vs Disease-Modifying Therapy. Median follow-up time was 24 months (interquartile range, 12-48 months).

Figure1: summary results from the MIST trial

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

University of Sheffield researchers in **bold.**

R1. **Snowden, J. A.**, Pearce, R. M., Lee, J., Kirkland, K., Gilleece, M., Veys, P., Clark, R. E., Kazmi, M., Abinun, M., Jackson, G. H., Mackinnon, S., Russell, N. H., & Cook, G. (2012). Haematopoietic stem cell transplantation (HSCT) in severe autoimmune diseases: analysis of UK outcomes from the British Society of Blood and Marrow Transplantation

(BSBMT) data registry 1997-2009. *British Journal of Haematology, 157*(6), 742–746. https://doi.org/10.1111/j.1365-2141.2012.09122.x

R2. Burt, R. K., Balabanov, R., Han, X., **Sharrack, B.**, Morgan, A., Quigley, K., Yaung, K., Helenowski, I. B., Jovanovic, B., Spahovic, D., Arnautovic, I., Lee, D. C., Benefield, B. C., Futterer, S., Oliveira, M. C., & Burman, J. (2015). Association of Nonmyeloablative Hematopoietic Stem Cell Transplantation With Neurological Disability in Patients With Relapsing-Remitting Multiple Sclerosis. *JAMA, 313*(3), 275. https://doi.org/10.1001/jama.2014.17986

R3. Muraro, P. A., Pasquini, M., Atkins, H. L., Bowen, J. D., Farge, D., Fassas, A., Freedman, M. S., Georges, G. E., Gualandi, F., Hamerschlak, N., Havrdova, E., Kimiskidis, V. K., Kozak, T., Mancardi, G. L., Massacesi, L., Moraes, D. A., Nash, R. A., Pavletic, S., Ouyang, J., … Saccardi, R. **The MS-AHSCT Long-Term Outcomes Study Group** (2017). Long-term Outcomes After Autologous Hematopoietic Stem Cell Transplantation for Multiple Sclerosis. *JAMA Neurology, 74*(4), 459. https://doi.org/10.1001/jamaneurol.2016.5867

R4. Burt, R. K., Balabanov, R., Burman, J., **Sharrack, B.**, **Snowden, J. A.**, Oliveira, M. C., Fagius, J., Rose, J., Nelson, F., Barreira, A. A., Carlson, K., Han, X., Moraes, D., Morgan, A., Quigley, K., Yaung, K., Buckley, R., Alldredge, C., Clendenan, A., … Helenowski, I. B. (2019). Effect of Nonmyeloablative Hematopoietic Stem Cell Transplantation vs Continued Disease-Modifying Therapy on Disease Progression in Patients With Relapsing-Remitting Multiple Sclerosis. *JAMA, 321*(2), 165. https://doi.org/10.1001/jama.2018.18743

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

Based on the research of Professors Snowden and Sharrack, AHSCT is now the “standard of care” in clinical practice as recommended through public policy changes with direct benefits to patients worldwide and reduced costs to the NHS.

Impact on national and international public policy

The Sheffield research [R1-4] has provided an evidence base for national and international professional society guidelines, position statements and recommendations on the use of AHSCT for MS and other ADs, which has extended the reach of the impact to the global level. As a core member of the Joint Accreditation Committee-ISCT & European Society for Blood and Marrow Transplant (EBMT), Snowden contributed to the EBMT consensus guidelines for immune monitoring and biobanking [S1] and produced general guidance for patients, families and carers considering hematopoietic stem cell transplantation [S3]. As a member of the Transplant Center and Recipient Issues Standing Committee for the Worldwide Network for Blood and Marrow Transplantation, Snowden also participated in developing their 2019 recommendations for establishing a hematopoietic stem cell transplantation program [S2]. In 2019, Sharrack coordinated the EBMT consensus guidelines on the use of HSCT in neurological immune-mediated disorders [S4].

Based on the results of the MIST trial, AHSCT has been approved as a treatment for RRMS in Wales, Scotland and is now provided through the NHS England commissioning route [S5]. The Belgian consensus protocol for autologous haematopoietic stem cell transplantation in MS was also informed by the Sheffield research [R4] and the EBMT guidelines [S6]. The American Society for Blood and Marrow Transplantation quoted the MIST study when revising the recommended indication for AHSCT in MS from ‘developmental’ to ‘standard of care, clinical evidence available’ for patients with relapsing forms of MS (RRMS or progressive MS with superimposed activity) [S6].

Impact on clinical practice

As a result of the changes in guidelines underpinned by the Sheffield research, the use of AHSCT in the treatment of ADs has increased by approximately one-third since 2016. The majority of this increase relates to the treatment of RRMS [S4].

Impact on patient quality of life and public understanding

Direct and long-lasting impact has been achieved for the patients who participated in the MIST trial [R4]. As noted in Section 2, 68–70% of the AHSCT-treated patients showed no evidence of disease activity, and progression-free survival was achieved in 70%–91% of these patients.

The improvement in patient quality of life after AHSCT is described by the recipients interviewed by the media. In a BBC Panorama documentary (2.5 million viewers) and major newspapers [S7], one patient who was wheelchair bound after the birth of her daughter reported that this new treatment has transformed her life. "*It worked wonders*," she said. "*I remember being in the hospital... after three weeks, I called my mum and said: 'I can stand'. We were all crying. I can run a little bit, I can dance. I love dancing, it is silly but I do. I enjoy walking my daughter around the park in her pram. It is a miracle but I can do it all*." Another patient, who had active MS, remained relapse free for three years after having AHSCT. He said, "*Several of my symptoms have now disappeared – I no longer get spasms that go down my spine when I flex my head forward, and my right leg hasn't given way for three years*."

The Sheffield team who pioneered this treatment for people living with MS has been recognised by the 2019 National Future NHS Parliamentary Award for their research having a life-changing impact "*on a number of patients who previously failed to respond to standard therapies, with some now being able to walk, run and even dance as a result of being involved in the trial*" [S8]. With other neuroscience researchers, the team received the national 2020 Queen Anniversary Award for research that has improved patient outcomes for people living with some of the most devastating neurodegenerative diseases [S8] and an international 2020 Clinical Research Forum (USA) Top Ten Research Achievement Award which honours outstanding accomplishments in clinical research [S8].

In further recognition of the benefit from AHSCT in RRMS, national and international patient organizations such as the MS Societies in the UK and US/Canada and the NHS directly refer to the MIST study in their patient information pages to help them make treatment decisions [S9].

Impact on health economics

Approximately 18,800 people in England are eligible for treatment with AHSCT. The recurring annual cost for the previous best available treatments is £15,000-£35,000 per patient, whereas the one-time cost for the AHSCT procedure is £30,000 (these estimates exclude clinical care costs). In the USA annual costs for DMT per patient are $80,000-100,000 compared to the one of cost of $85,184 for AHSCT. Therefore, although the initial costs may be similar, the cost savings for Healthcare providers continue to accumulate [S10].

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

S1. Alexander, T. et. al. (2014). SCT for severe autoimmune diseases: consensus guidelines of the European Society for Blood and Marrow Transplantation for immune monitoring and biobanking. *Bone Marrow Transplantation, 50*(2), 173–180. https://doi.org/10.1038/bmt.2014.251

S2. Pasquini, M. C. et. al. (2019). Worldwide Network for Blood and Marrow Transplantation Recommendations for Establishing a Hematopoietic Cell Transplantation Program, Part I:

Minimum Requirements and Beyond. *Biology of Blood and Marrow Transplantation, 25*(12), 2322–2329. https://doi.org/10.1016/j.bbmt.2019.05.002

S3. Jessop, H. et. al. (2019). General information for patients and carers considering haematopoietic stem cell transplantation (HSCT) for severe autoimmune diseases (ADs): A position statement from the EBMT Autoimmune Diseases Working Party (ADWP), the EBMT Nurses Group, the EBMT Patient, Family and Donor Committee and the Joint Accreditation Committee of ISCT and EBMT (JACIE). *Bone Marrow Transplantation, 54*(7), 933–942. https://doi.org/10.1038/s41409-019-0430-7

S4. Sharrack, B. et. al. (2019). Autologous haematopoietic stem cell transplantation and other cellular therapy in multiple sclerosis and immune-mediated neurological diseases: updated guidelines and recommendations from the EBMT Autoimmune Diseases Working Party (ADWP) and the Joint Accreditation Committee of EBMT and ISCT (JACIE). *Bone Marrow Transplantation, 55*(2), 283–306. https://doi.org/10.1038/s41409-019-0684-0

S5. Commission approvals for use of AHSCT as treatment for RRMS: Health Technology Wales; Healthcare Improvement Scotland; NICE Guidance ID111.

S6. International clinical guidelines adopting AHSCT for treating RRMS as Standard of Care:

- A Belgian consensus protocol for autologous haematopoietic stem cell transplantation in multiple sclerosis (2018). http://hdl.handle.net/2268/232296
- Cohen, J. A. et. al. (2019). Autologous Hematopoietic Cell Transplantation for Treatment-Refractory Relapsing Multiple Sclerosis: Position Statement from the American Society for Blood and Marrow Transplantation. *Biology of Blood and Marrow Transplantation, 25*(5), 845–854. https://doi.org/10.1016/j.bbmt.2019.02.014

S7. Combined: a selection of patient feedback on their improved quality of life captured in the media coverage that reached 180 million people worldwide. BBC 'Cancer treatment for MS patients gives 'remarkable' results' (https://www.bbc.co.uk/news/health-35065905) and Daily Telegraph 'Miracle' stem cell therapy reverses MS' (https://bit.ly/31b9RZZ).

S8. Combined: 2019/2020 awards for Sheffield research that has improved patient outcomes. Winners of the NHS Parliamentary Awards 2019 (https://www.england.nhs.uk/nhs-parliamentary-awards/about/winners/), Queen's Anniversary Prize (https://bit.ly/31fDLMK) and Clinical Research Forum's Top Ten Clinical Research Award (https://www.clinicalresearchforum.org/page/2020awardees).

S9. Information for patients with MS on AHSCT as a treatment:

- HSCT information for patients on MS Society (UK) website refers to MIST trial (https://www.mssociety.org.uk/about-ms/treatments-and-therapies/disease-modifying-therapies/hsct).
- National MS Society website (US/Canada) quotes MIST Trial (https://www.nationalmssociety.org/Research/Research-News-Progress/Stem-Cells-in-MS/Bone-Marrow-Stem-Cell-Transplant-%E2%80%93-HSCT).

S10. UK: NICE (2018) Block scoping report – Batch 62. Burt, R. K., Tappenden, P., Han, X., Quigley, K., Arnautovic, I., Sharrack, B., Snowden, J. A., & Hartung, D. (2020). Health economics and patient outcomes of hematopoietic stem cell transplantation versus disease-modifying therapies for relapsing remitting multiple sclerosis in the United States of America. *Multiple Sclerosis and Related Disorders, 45*, 102404. https://doi.org/10.1016/j.msard.2020.102404