The role of salvage autologous stem cell transplantation (sASCT) in relapsed multiple myeloma (MM)

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“There is no harm in repeating a good thing.”

Plato

(429 -345 BC)

Philosopher, Ancient Greece

Abstract of Thesis

The use of high dose chemotherapy and autologous stem cell transplantation (ASCT) is standard of care first-line therapy for multiple myeloma (MM) in suitably fit patients. In the relapse setting after a prior ASCT, the use of a second or salvage ASCT (sASCT) evolved without randomised controlled trial evidence of clinical effectiveness, largely based on evidence from retrospective registry or single centre studies, and 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. After a thorough exploration of the unmet need in this area of clinical practice, I designed the first retrospective national, case-matched control analysis on patients who underwent sASCT compared with conventional chemotherapy, and found improved progression-free and overall survival compared with conventional chemotherapy. 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, I designed, led and delivered the NCRI-badged UK Myeloma Forum Myeloma X study, funded by Cancer Research UK. This multi-centre, phase III study investigated the role of sASCT as management of first relapsed disease in patients relapsing after a standard first-line ASCT, versus a non-ASCT consolidation, which was standard of care at the time of study set-up and initiation. All patients received a modern-day re-induction regimen for the era of the trial and the trial outcomes sought to influence clinical practice. Additionally, the study explored whether stem cells could be harvested after a prior ASCT, which would otherwise limit the adoption of sASCT in *real-world* practice. The trial (Myeloma X) provided the first and only global clinical evidence for the benefits of sASCT for relapse

MM. In addition, the study defined that the advantages demonstrated by sASCT did not compromise quality of life. Consequentially, sASCT was adopted in national and international guidelines, accepted for reimbursement and has been pivotal to formulating the clinical practice internationally.

The outputs have resulted in a measurable change in clinical practice and it is estimated that over 100 patients a year in the US have benefitted from this treatment as a consequence of the published trial outcomes, with similar benefits having been reported in France and other European countries. Taken together, the results of this trial have had an impact on the clinical management pathway in MM and helping the decision-making process for both physicians and myeloma patients.

The evidence presented in this thesis represents peer-reviewed publications derived from this late phase, practice-changing clinical trial.

Thesis Word Count: 18,682 words

Declaration

I hereby declare that the work presented in this thesis is my own, except where stated in the text. The work has not been submitted in any previous application for a degree.

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	Appendix 6 - RM de Tute*, **G Cook***, JM Brown, J Cavenagh, AJ Ashcroft, JA Snowden, C Williams, K Yong, E Tholouli, M Jenner, A Hockaday, MT Drayson, TCM Morris, AC Rawstron, DA Cairns & RG Owen, on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. Impact of minimal residual disease (MRD) in relapsed myeloma: results from the NCRI Myeloma X (intensive) trial. (Submitted to *Bone Marrow Transplantation* 2023)	

Included Publications

Chapter 1	**G Cook** & TCM Morris. (2020) Evolution or revolution in Multiple Myeloma therapy and the role of the UK. *British Journal of Haematology*, 191, 4, 542. doi: 10.1111/bjh.17148. **Impact Factor:** 8.615 **Role:** I designed the manuscript plan and wrote the first draft, and approved the final version as lead author. **G Cook** , GH Jackson, GJ Morgan, NH Russell, K Kirkland, J Lee, DI Marks & A Pagliuca A. (2011) The outcome of high dose chemotherapy and autologous stem cell transplantation (ASCT) in patients with multiple myeloma: a comparison between two decades and benchmarking against European outcomes. *Bone Marrow Transplantation* 46(9):1210-8. **Impact Factor:** 5.483 **Role:** I designed the study, collected the data, analyzed the data in collaboration and wrote the manuscript as lead author. GH Jackson, FE Davies, C Pawlyn, DA Cairns, A Striha, C Collett, A Waterhouse, JR Jones, B Kishore, MGarg, CD Williams, K Kar unanithi, J Lindsay, D Allotey, S Shafeek, MW Jenner, **G Cook**, NH Russell, MF Kaiser, MT Drayson, RG Owen, WM Gregory & GJ Morgan. (2021) Lenalidomide Before And After ASCT For Transplant-Eligible Patients Of All Ages In The Randomized, Phase III, Myeloma XI Trial. *Haematologica*. haematol.2020.247130; **Doi:**10.3324/haematol.2020.247130 **Impact Factor:** 7.57 **Role:** I was a member of the Trial Management Group (Myeloma XI) that designed the study, collected and analyzed the data and drafted/approved the final version of the manuscript. C Pawlyn, DA Cairns, T Menzies, J Jones, M Jenner, **G Cook**, K Boyd, M Drayson, M Kaiser, RG Owen, W Gregory, G Morgan, G Jackson & FE Davies. (2022) Autologous stem cell transplant is

	safe and effective for fit older myeloma patients. *Haematologica* doi.org/10.3324/haematol.2020.262360 **Impact Factor:** 7.57 **Role:** I was a member of the Trial Management Group (Myeloma XI) that designed the study, collected and analyzed the data and drafted/approved the final version of the manuscript. RM de Tute, C Pawlyn, DA Cairns, FE Davies, T Menzies, A Rawstron, JR Jones, A Hockaday, R Henderson, **G Cook**, MT Drayson, MW Jenner, MF Kaiser, WM Gregory, GJ Morgan, GH Jackson & RG Owen. (2022) Minimal residual disease following autologous stem cell transplant for myeloma patients: prognostic significance and the impact of lenalidomide maintenance and molecular risk. *Journal of Clinical Oncology* DOI: 10.1200/JCO.21.02228 **Impact Factor:** 44.57 **Role:** I was a member of the Trial Management Group (Myeloma XI) that designed the study, collected and analyzed the data and drafted/approved the final version of the manuscript.
Chapter 2	C Parrish, J Apperley, A Bloor, R Pearce, K Kirkland, J Lee, C Craddock, K Wilson & **G Cook**. (2015) On behalf of the British Society of Bone Marrow Transplantation Clinical Trials Committee The Role of High Dose Chemotherapy and Autologous Stem Cell Transplantation in Patients with Multiple Myeloma Refractory to Initial Induction Therapy. *Biology of Bone Marrow Transplantation*. doi 10.1016/j.bbmt.2015.03.026 **Impact Factor:** 7.57 **Role:** I designed the study, collected the data, analyzed the data in collaboration and wrote the manuscript as lead author. **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 **Impact Factor:** 5.609 **Role:** I designed the study, collected the data, analyzed the data in collaboration and wrote the manuscript as lead author. TCM Morris*, **G Cook***, M Streetly, P Kettle, M Drake, M Quinn, J Cavet, J Tighe, M Kazmi, J Ashcroft, M Cook, J Snowden, A Olujohungbe, S Marshall, J Conn, H Oakervee, R Popat & J

	Cavenagh. (2011) Re-transplantation after Bortezomib-based therapy. *British Journal of Haematology* 153(5):666-8 **Impact Factor:** 8.615 **Role:** I designed the study and manuscript plan, wrote the first draft, and approved the final version as co-lead author.
Chapter 3	TCM Morris, C Williams, S Bell, M Fletcher, A Szubert, J Cavenagh, J Snowden, J Ashcroft, K Yong, J Cavet, J Brown & **G Cook**. (2013) Patient perceptions of second transplants in myeloma: impact on recruitment in the BSBMT/UKMF Myeloma X Relapse (Intensive) Trial. *British Journal of Haematology*, 163, 4, 541-3. **Impact Factor:** 8.615 **Role:** I designed the study, collected the data, analyzed the data in collaboration and wrote the manuscript as senior author. **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) A Second Autologous Stem Cell Transplant Induces Superior Durability of Response following Bortezomib-containing Re-induction Therapy for Relapsed Multiple Myeloma (MM): Final Results from the BSBMT/UKMF Myeloma X (Intensive) Trial. *The Lancet Oncology,* Vol. 15, No. 8, p874–885. **Impact Factor:** 41.32 **Role:** I designed the study, collected the data, analyzed the data in collaboration and wrote the manuscript as lead author. **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) The impact of salvage autologous stem cell transplantation on overall survival in patients with relapsed multiple myeloma: Final results from the BSBMT/UKMF Myeloma X Relapse (Intensive) randomised open-label phase 3 trial. *The Lancet Haematology*, 3, 7; e340–e351 **Impact Factor:** 18.60 **Role:** I designed the study, collected the data, analyzed the data in collaboration and wrote the manuscript as lead author. 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

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Chapter 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, 450-67 doi/10.1111/bjh.15782 **Impact Factor:** 8.615 **Role:** I designed the study, collected the data, analyzed the data in collaboration and wrote the manuscript as lead author. SH Ahmedzai, JA Snowden, AJ Ashcroft, DA Cairns, C Williams, A Hockaday, JD Cavenagh, C Parrish, JM Brown, TCM Morris & **G Cook** on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. (2019) The effect of salvage autologous stem-cell transplantation on patient-reported outcomes in relapsed multiple myeloma: results from NCRI Myeloma X Relapse [Intensive]): randomised phase 3 trial. *Journal of Clinical Oncology 37, 19, 1617-28* DOI: 10.1200/JCO.18.01006. **Impact Factor:** 44.57 **Role:** I designed the study, collected the data, analyzed the data in collaboration and wrote the manuscript as senior author. J Snowden, S Ahmedzai, A Cox, DA Cairns, AJ Ashcroft, C Williams, J Cavenagh, A Hockaday, J Brown, I Brock, TCM Morris & **G Cook**. (2022) Association of Genetic Variants with Patient Reported Quality of Life and Pain Experience in patients in the UK NCRI Myeloma X Relapse [Intensive]) trial; an exploratory study. *Bone Marrow Transplantation* doi: 10.1038/s41409-022-01738-y **Impact Factor:** 5.483

	Role: I designed the study, collected the data, analyzed the data in collaboration and wrote the manuscript as senior author.
Chapter 5	S Giralt, L Garderet, B Durie, **G Cook**, G Gahrton, B Bruno, P Hari, H Lokhorst, P McCarthy, A Krishnan, P Sonneveld, H Goldschmidt, S Jagannath, B Barlogie, M Mateos, P Gimsing, O Sezer, J Mikhael, L Jin, M Dimopoulos, A Mazumder, A Palumbo, R Abonour, K Anderson, M Attal, J Blade, J Bird, M Cavo, R Comenzo, J de la Rubia, H Einsele, R Garcia Sanz, J Hillengass, S Holstein, H Johnsen, D Joshua, G Koehne, S Kumar, R Kyle, X Leleu, S Lonial, H Ludwig, H Nahi, A Nooka, R Orlowski, V Rajkumar, A Reiman, P Richardson, E Rivas, J San Miguel, I Turreson, S Usmani, D Vesole, W Bensinger, M Qazilbash, Y Efebera, M Mohty, C Gasparreto, J Gajewski, C LeMaistre, C Bredeson, P Moreau, M Pasquini, N Kroeger, & E Stadtmauer. (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. *Biol Bone Marrow Transplantation* 21(12):2039-51 doi: 0.1016/j.bbmt.2015.09.016. **Impact Factor:** 5.609 **Role:** As the UK lead for ASCT in myeloma, I collated the evidence for sASCT in myeloma, and wrote the international guidelines section for sASCT. I wrote the manuscript as a co-author. P Moreau, SK Kumar, J San Miguel, F Davies, E Zamagni, N Bahlis, H Ludwig, J Mikhael, E Terpos, F Schjesvold, T Martin, K Yong, BGM Durie, T Facon, A Jurczyszyn, S Sidana, N Raje, N van de Donk, S Lonial, M Cavo, SY Kristinsson, S Lentzsch, R Hajek, KC Anderson, C Joao, H Einsele, P Sonneveld, M Engelhardt, R Fonseca, A Vangsted, K Weisel, R Baz, V Hungria, JG Berdeja, FL da Costa, A Maiolino, A Waage, D Vesole, E Ocio, H Quach, C Driessen, J Bladé, X Leleu, E Riva, N Abilgaard, L Bergsagel, L Hou, W Joo Chng, U-H Mellqvist, D Dytfeld, J-L Harousseau, H Goldschmidt, J Laubach, N Munshi, F Gay, M Beksac, LJ Costa, M Kaiser, P Hari, M Boccadoro, SZ Usmani, S Zweegman, S Holstein, O Sezer, S Harrison, H Nahi, **G Cook**, M-V Mateos, S.V Rajkumar, MA Dimopoulos & PG Richardson. (2021) International Myeloma Working Group (IMWG) recommendations for the treatment of relapsed and refractory multiple myeloma. *Lancet Oncology*, 22(3):e105-e118 01 **Impact Factor:** 41.32

	Role: As the UK lead for ASCT in myeloma, I collated the evidence for sASCT in myeloma, and wrote the guidelines section for sASCT. I co- wrote the manuscript as a co-author. MA Dimopoulos, P Moreau, E Terpos, MV Mateos, S Zweegman, **G Cook**, M Delforge, R Hajek, F Schjesvold, M Cavo, H Goldschmidt, T Facon, H Einsele, M Boccadoro, J San-Miguel, P Sonneveld & U Mey, on behalf of the EHA Board and the ESMO Guidelines Committee. (2021) Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up *Annals of Oncology*. doi.org/10.1016/j.annonc.2020.11.014 **Impact Factor:** 32.98 **Role:** As the UK myeloma key opinion leader, I was a member of the guidelines committee who reviewed the evidence for myeloma treatment, and l conducted the evidence collation for sASCT in myeloma in particular, and wrote the guidelines section for sASCT. I wrote the manuscript as a co-author. B Dhakal, N Shah, A Kansagra, A Kumar, S Lonial, Al Garfall, A Cowan, B Sharma Poudyal, C Costello, F Gay, **G Cook**, H Quach, H Einsele, J Schriber, J Hou, L Costa, M Aljurf, M Chaudhry, M Beksac, M Prince, M Mohty, M Janakiram, N Callander, N Biran, P Malhotra, P Rodriguez Otero, P Moreau, R Abonour, R Iftikhar, R Silberman, S Mailankody, T Gregory, Y Lin, P Carpenter, M Hamadani, S Usmani & S Kumar. (2022) ASTCT Clinical Practice recommendations for transplant and cellular therapies in multiple myeloma. *Transplantation and Cellular Therapy* doi: /10.1016/j.jtct.2022.03.019 **Impact Factor:** 5.609 **Role:** As the UK lead for ASCT in myeloma, I reviewed and collated the evidence for sASCT in myeloma, and wrote the up-dated international guidelines section for sASCT. I co- wrote the manuscript as a co-author.
Chapter 6	**G Cook**. (2015) Re-invigorating rather than re-inventing the wheel: Augmenting the impact of salvage autologous stem cell transplantation for multiple myeloma in the era of novel agents. *Bone Marrow Transplantation,* 50(10):1269-70. **Impact Factor:** 5.483 **Role:** I wrote the manuscript as senior author. A Striha, AJ Ashcroft, A Hockaday, DA Cairns, K Boardman, G Jacques, C Williams, J Snowden, J Cavenagh, K Yong, M Drayson, R Owen, M Cook & **G Cook**. (2018) The role of ixazomib as an augmented conditioning therapy in salvage autologous stem cell transplant (ASCT) and as a post-ASCT

	consolidation and maintenance strategy in patients with relapsed multiple myeloma: the phase III ACCoRd (Myeloma XII) study protocol. *Trials* 19(1):169 doi: 10.1186/s13063-018-2524-8. **Impact Factor:** 5.609 **Role:** I designed the study, lead the Trial Management Group as Chief Investigator and responsible for data collection. I wrote the manuscript as senior author. RJ Brownlie, R Kennedy, M Milanovic, EB Wilson, CF Taylor, D Wang, JR Davies, H Owston, EJ Adams, S Stephenson, R Caeser, DJ Hodson, PV Giannoudis, C Scuoppo, D McGonagle, RM Tooze, GM Doody, **G Cook**, DR Westhead & U Klein. (2023) Cytokine receptor IL27RA is an NF-κB-responsive gene involved in CD38 upregulation in multiple myeloma. *Blood Advances* doi 10.1182/bloodadvances.2022009044 **Impact Factor:** 25.46 **Role:** I co-designed the study, supplied the samples, assisted in the data interpretation and manuscript writing.

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tolerated in relapsed or refractory multiple myeloma regardless of patient age: subgroup analysis of the phase 3 CASTOR and POLLUX studies. *Haematologica* 105 (2) 468-477; DOI: 10.3324/haematol.2019.217448

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Munshi &H Avet-Loiseau. (2020) Clinical Features Associated with SARS-CoV-2 Outcome in Multiple Myeloma: International Myeloma Society COVID-19 Registry Results. *Blood*, doi.org/10.1182/blood.2020008150

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Figures and Tables

Figure 1

Acknowledgments

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I wish to acknowledge the assistance given to me by the leadership and colleagues in the Leeds Institute of Clinical Trial Research, especially Professor Julia Brown and Dr David Cairns, who have supported me in my academic career. I would like to thank the members of the trial management groups for the NCRI Myeloma X and UKMRA Myeloma XII trials; without their efforts and devotion these trials would not be delivered to impact on clinical care. I would like to thank all the patients, carers and staff involved in these trials throughout the United Kingdom.

Finally, to my wife Julianne and daughters, Gemma and Amy, for all their patience and understanding throughout my career. I am eternally grateful and love them dearly.

I dedicate this thesis to Mr Stan Dagg (1940-2015), who like many before and after him, suffered from Multiple Myeloma. R.I.P.

Chapter 1

Introduction

Multiple Myeloma (MM), an incurable malignancy of mature B-cells and the knowledge of disease biology as well as the therapeutic landscape in MM has expanded exponentially in recent years. The impact on patient survivorship is clear to see through the decades, consequential to clinical trial delivery, not only academic but industry-driven trials incorporating novel, targeted therapies. Through reverse translational research, we have evolved our knowledge of the sub-cellular processes, including proteostasis and molecular genomics, that drive the disease paving the way to better treatment strategies and identifying areas of clinical unmet need. The improvements in survivorship, not only in the clinical trial setting but also in the *real-world* setting are tangible for patients and their families and more importantly there is also every evidence to indicate that such improvements in our understanding and treatments will continue.

1.1 Multiple Myeloma: A Historical perspective and Clinical-pathological Features.

Plasma cell dyscrasias are a heterogeneous group of disorders that are characterised by the clonal expansion of terminally differentiated B cells. MM was first reported by Dr Samuel Solly in his communication to the Royal Medical Chirurgical Society in London(1) though Dr William MacIntyre is frequently credited with the first description when he reported a case of light chain MM(2). However, it wasn't until 1873 that the disease was referred to as *Multiple Myeloma* by Dr Rustizky to indicate the multiple nature of the bone marrow tumours(3). In 1900, Dr Wright discovered that the homogeneous cellular

infiltrate seen in the bone marrow (BM) of patients with MM was in fact a tumour of plasma cells (Figure 1.1). Early therapeutic interventions ranging from rhubarb and orange peel infusions to therapeutic venesection, quinine, camphor, Dover's powders and urethane, were of limited value (4). Melphalan, had been introduced for MM in the early 1960s but for haematologists, MM was still considered the 'heart sink' disease as responses were limited with treatment toxicities (cytopenias) and disease-related morbidity being significant issues.

The plasma cell infiltration of BM is largely diagnosed through morphological examination of BM aspirates (Figure 1.1), although increasingly the use of plastic-embedded biopsy sections, multi-parameter flow cytometry, fluorescence *in situ* hybridisation studies and cross-sectional imaging (magnetic resonance imaging, PET/CT scanning) provide a measure of global disease burden as well as high risk clinical-genomic features. A diagnosis of MM is made using the criteria proposed in 2003 by the International Myeloma Working Group (IMWG), updated in the European Society of Medical Oncology guidelines in 2017 and referenced in the 2021 update, detailed in Table 1.1 (5). Symptomatic MM is defined by the presence of MM-related organ or tissue impairment (ROTI), as defined in Table 1.2. These clinical-laboratory parameters are referred to as CRAB criteria (hyper**c**alcaemia, **r**enal impairment, **a**naemia, **b**one disease).

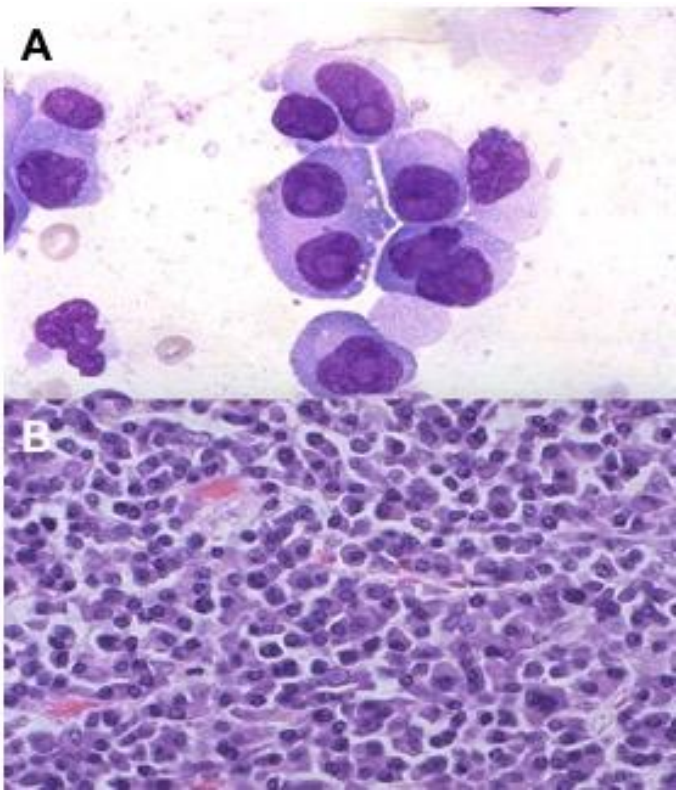

Figure 1.1 Bone marrow plasma cell infiltrate in multiple myeloma. The morphology of bone marrow aspirate (A- Geimsa, X400) and histology of paraffin-embedded marrow trephine biopsy (B- H&E, X200) demonstrate atypical plasma cells with bi-nucleate forms and prominent nucleoli easily identified.

Monoclonal Gammopathy of Undetermined Significance (MGUS)	**Asymptomatic myeloma**	**Symptomatic myeloma**
M-protein in serum <30 g/l	M-protein in serum ≥30 g/l and/or Bone marrow clonal plasma cells ≥10 %	M-protein in serum and/or urine**
Bone marrow clonal plasma cells <10 % and low level of plasma cell infiltration in a trephine biopsy (if done)		Bone marrow (clonal) plasma cells or biopsy proven plasmacytoma
No related organ or tissue impairment ((no end organ damage including bone lesions)	No related organ or tissue impairment (no end organ damage including bone lesions) or symptoms	Myeloma-related organ or tissue impairment (including bone lesions)

Table 1.1 Laboratory diagnostic criteria to define MGUS from MM. **No specific concentration required for diagnosis. A small percentage of patients have no detectable M-protein in serum or urine but do have myeloma-related organ impairment (ROTI) and increased bone marrow plasma cells (non-secretory myeloma).

Clinical effects due to myeloma	**Definition**
*Increased calcium levels	Corrected serum calcium >0.25mmol/l above the upper limit of normal or >2.75mmol/l
*Renal insufficiency	Creatinine>173mmol/l
*Anaemia	Haemoglobin 2 g/dl below the lower limit of normal or haemoglobin <10 g/dl
*Bone lesions	Lytic lesions or osteoporosis with compression fractures (MRI or CT may clarify)
Other	Symptomatic hyperviscosity, amyloidosis, recurrent bacterial infections (> 2 episodes in 12 months)

Table 1.2 Laboratory criteria to MM-related organ or tissue impairment (ROTI) that defines symptomatic disease from smouldering MM. *Hypercalcaemia, renal impairment, anaemia and be disease are recognised as CRAB.

MM accounts for 1-1.8% of all cancers and is the second most common haematological malignancy with an estimated incidence in Europe of 4.5-6.0/100 000/year(6). MM often presents with both vague and non-specific symptoms, creating a diagnostic challenge. Consequently, the diagnosis of MM is frequently made via emergency services and may follow multiple prior consultations with medical professionals. In the 1960s, the disease presented most commonly with back pain, reported in up to 70% of patients. The National Cancer Intelligence Network (NCIN) *Routes To Diagnosis* report identified that 32% of myeloma diagnoses in 2013 were made via emergency care, with these emergency presentations being associated with shorter survival (7, 8). Furthermore, patients presenting via the emergency route are more likely to have more CRAB features or higher International Staging System (ISS) scores, indicating a higher burden of disease (6). Despite the significant improvement in patients' survival over the past 20 years, only 10%-15% of patients achieve or exceed expected survival compared with the matched general population(6).

1.2 Treatment Landscape in Multiple Myeloma

Therapy advances in MM have greatly expanded since the serendipitous finding of the anti-myeloma efficacy of thalidomide in 1999. The treatment landscape in MM and how the UK clinical-academic community has contributed is exemplified in the first publication included in this thesis (9). This publication is not intended to be a comprehensive review of treatment but instead aims to give a temporal context to these developments, highlighting the contribution of UK clinicians, healthcare workers, scientists and most importantly patients and their relatives have played in this revolution.

High dose cytoreductive therapy with autologous hematopoietic stem cell rescue (ASCT) is able to provide significant disease controlling effect in a number of hematologic malignancies. ASCT was introduced in the treatment of MM in the 1980s (10, 11) and with the introduction of the use of peripheral blood stem cells instead of bone marrow in the 1990s markedly improved the feasibility and safety profile (12). In fit patients who have normal renal function and are younger than 65 years of age, randomized studies have shown the superiority of ASCT compared with conventional chemotherapy as up-front disease management in myeloma (13-15), and thus in Europe and the United States, ASCT in first line treatment is considered the standard of care (SoC) for patients with MM and accounts for nearly 50% of ASCT performed in Europe and United States(16).

The second publication reflects the *real-world* utility of ASCT in first line treatment of newly diagnosed MM patients and how the outcomes have changed before and after the introduction of novel, more targeted agents (<1999 versus >2000), namely the introduction of thalidomide, with the analysis incorporating a benchmarking exercise defining the outcomes in the United Kingdom by comparison to the rest of Europe(17).

1.3 National Cancer Research Institute (NCRI) Myeloma XI trial

The NCRI Myeloma XI was a phase III, open-label, parallel-group, multi-arm, adaptive design trial with three randomization stages conducted at 110 National Health Service hospitals in England, Scotland and Wales (EudraCT number, 2009-010956-93), funded by Cancer Research UK and industry partnerships. It is the world's largest frontline, late phase trial in MM. Eligible patients were aged ≥18 years and had untreated,

symptomatic MM. Patients who were young and fit enough to tolerate ASCT entered the intensive treatment pathway (i.e., transplant-eligible; TE). Older and less fit patients entered the non-intensive treatment pathway (i.e., transplant-noneligible; TNE). For the TE pathway, the trial incorporated the co-primary objectives of:

- comparing a thalidomide-containing regimen (CTD) with a lenalidomide-containing regimen (CRD), as induction treatment prior to ASCT, with respect to overall/progression-free survival and response.
- assessing response to a novel agent, bortezomib plus cyclophosphamide and dexamethasone (CVD), in participants whose response to induction treatment is sub-optimal (<VGPR).

A number of secondary and biological objectives were included. The trial recruited 4420 patients across both pathways from 2010-2016 and to-date, has produced 55 publications, >2,000 citations and the dataset has been utilised in several clinical prediction modelling studies including a patient vulnerability score (UKMRA Myeloma Risk Profile; MRP)(18) and in tumour genomic profiling(19) that have influenced the design of current trials (UKMRA Myeloma XIV FiTNEss and XV RADAR trials). The design of the TE pathway is illustrated in Figure 1.2 and a summary of the trial outputs and influence on current clinical and translational research is illustrated in Figure 1.3.

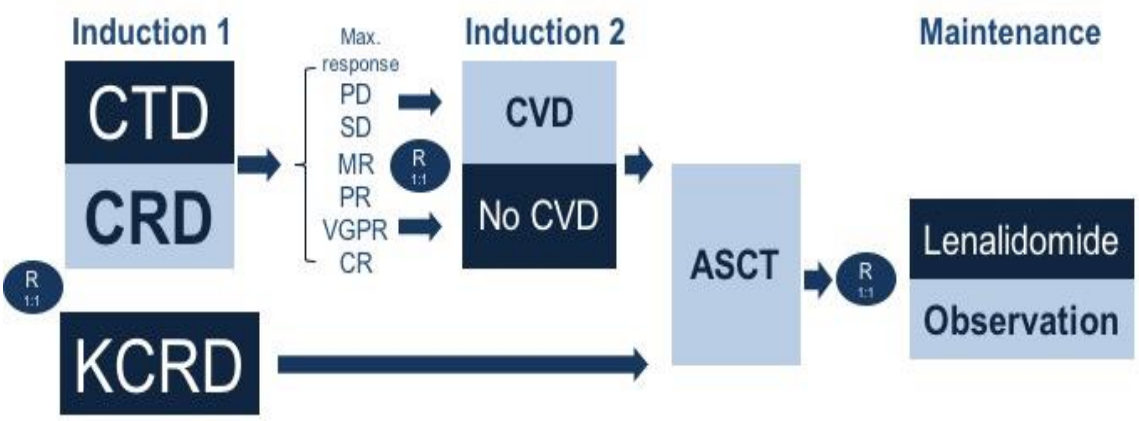

Figure 1.2 NCRI Myeloma XI Trial schema.
CTD- cyclophosphamide/thalidomide/dexamethasone;
CRD - cyclophosphamide/lenalidomide/dexamethasone;
KCRD- carfilzomib/cyclophosphamide/lenalidomide/dexamethasone;
CVD - cyclophosphamide/bortezomib/dexamethasone

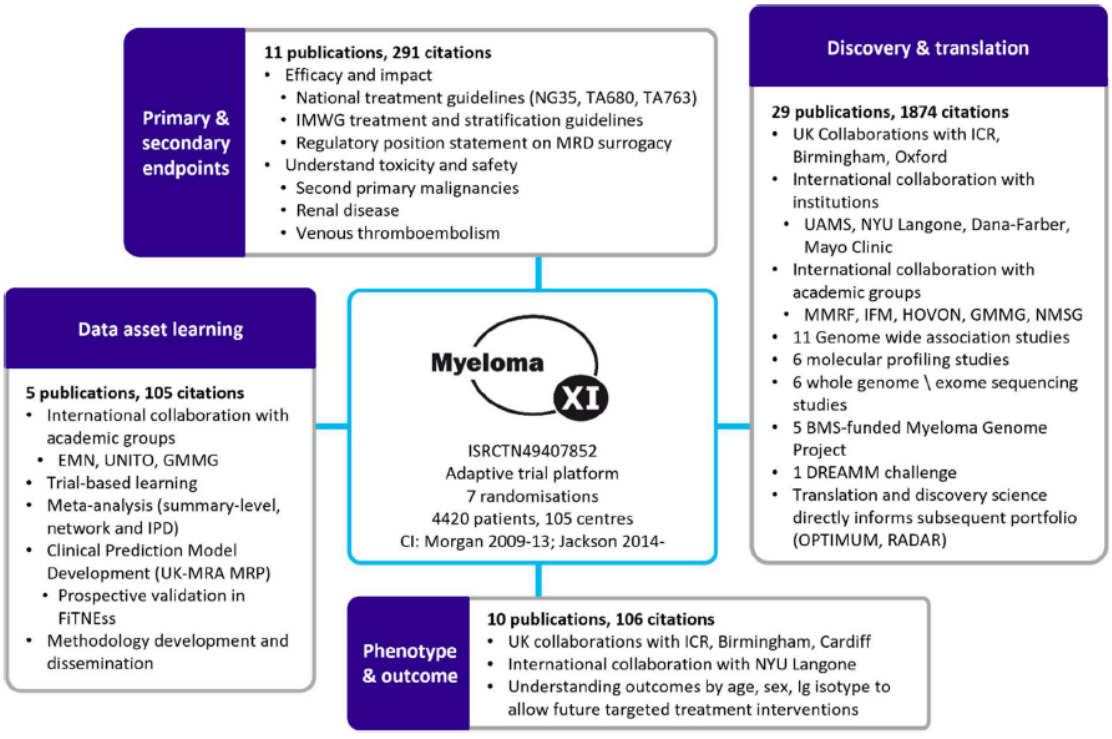

Figure 1.3 NCRI Myeloma XI Trial outputs (to date): Integrating primary and secondary trial design with discovery and data science

1.3 Publications

Three of the trial-related publications are especially important to the background of this thesis. The first publication highlights the influence of modern, novel agents specifically on patients undergoing ASCT, where the immunomodulatory drug (IMID), lenalidomide (Revlimid®), demonstrated an impact on disease response durability and survivorship when delivered before and after the ASCT(20), following the publication of the specific influence of lenalidomide as a maintenance strategy across both the TE and TNE pathways (21). This publication highlights the continued advantage of utilising an ASCT in first line therapy despite the evolution of novel biological targeted agents and their incorporation into MM treatment strategies.

The second publication is a post-trial analysis of the utility and safety of ASCT in older patients, examining what benefit such patients derive from an ASCT compared to less intensive treatment (22). This publication highlights the evolving opportunity to use ASCT in the older person, having previously been relatively age-restricted. Thus more patients have the potential to gain benefit from ASCT in first line therapy and recent evidence highlights the rapid growth in ASCT utility in the older person across Europe(23).

The third publication reflects the central importance of minimal residual disease (MRD) measurement as a treatment response biomarker, from discovery to validation of treatment outcomes, including OS(24). The Myeloma XI publication highlights the extent that sustainable MRD negativity contributes to the overall response durability (PFS) and survivorship (OS) in the setting of maintenance therapy after an ASCT in front line therapy(25).

1. **G Cook** & TCM Morris. (2020) Evolution or revolution in Multiple Myeloma therapy and the role of the UK. *British Journal of Haematology*, 191, 4, 542. doi: 10.1111/bjh.17148.

2. **G Cook** , GH Jackson, GJ Morgan, NH Russell, K Kirkland, J Lee, DI Marks & A Pagliuca A. (2011) The outcome of high dose chemotherapy and autologous stem cell transplantation (ASCT) in patients with multiple myeloma: a comparison between two decades and benchmarking against European outcomes. *Bone Marrow Transplantation* 46(9):1210-8.

3. GH Jackson, FE Davies, C Pawlyn, DA Cairns, A Striha, C Collett, A Waterhouse, JR J ones, B Kishore, MGarg, CD Williams, K Karunanithi, J Lindsay, D Allotey, S Shafeek, MW Jenner, **G Cook**, NH Russell, MF Kaiser, MT Drayson, RG Owen, WM Gregory & GJ Morgan. (2021) Lenalidomide Before And After ASCT For Transplant-Eligible Patients Of All Ages In The Randomized, Phase III, Myeloma XI Trial. *Haematologica*. haematol.2020.247130; **Doi:**10.3324/haematol.2020.247130

4. C Pawlyn, DA Cairns, T Menzies, J Jones, M Jenner, **G Cook**, K Boyd, M Drayson, M Kaiser, RG Owen, W Gregory, G Morgan, G Jackson & FE Davies. (2022) Autologous stem cell transplant is safe and effective for fit older myeloma patients. *Haematologica* doi.org/10.3324/haematol.2020.262360

5. RM de Tute, C Pawlyn, DA Cairns, FE Davies, T Menzies, A Rawstron, JR Jones, A Hockaday, R Henderson, **G Cook**, MT Drayson, MW Jenner, MF Kaiser, WM Gregory, GJ Morgan, GH Jackson & RG Owen. (2022) Minimal residual disease following autologous stem cell transplant for myeloma patients: prognostic significance and the impact of lenalidomide maintenance and molecular risk. *Journal of Clinical Oncology* DOI: 10.1200/JCO.21.02228

Taken together, these publications highlight the established role of ASCT in the management of newly diagnosed patients in the modern era of novel agent-directed therapy. The use of a second transplant after disease progression from a first ASCT, referred to as a salvage ASCT (sASCT) is a clinically attractive option but is there an evidence basis for this clinical strategy? Does it benefit all patients relapsing from a prior ASCT? What is the impact from a patient's perspective of sASCT? These questions form the basis of this thesis hypothesis.

1.4 Thesis Hypothesis and Aims

The thesis hypothesis is that a salvage high dose chemotherapy and autologous stem cell transplant can induce prolonged disease control and improve survivorship in selected patients with relapsed multiple myeloma. Therefore the aim of the published works presented in this thesis are to:

1. Establish the unmet clinical need of salvage ASCT in the therapeutic landscape of multiple myeloma.
2. To define the impact of salvage ASCT in disease control and survivorship in relapsed myeloma.
3. To define key patient sub-groups and the impact on Quality of Life.
4. To delineate the impact on *real-world* clinical practice arising from the Myeloma X trial

The included published works highlight the treatment landscape, the unmet need, how the NCRI Myeloma X trial answers that clinical question, including secondary endpoints

to further develop the clinical evidence, and the way forward in terms of the follow on trial , UKMRA Myeloma XII (ACCoRD) trial (finished recruitment in May 2022).

Chapter 2

The Unmet Need

2.1 Introduction

The introduction of ASCT for MM in the 1980s marked a breakthrough in the management of this mature B-cell malignancy. Results of randomised trials comparing high-dose therapy plus ASCT with conventional chemotherapy have shown that transplantation improves progression-free and overall survival(14). Consequentially, the procedure became standard of care for patients with chemo-responsive disease up to the age 65-70 years without substantial comorbidities. The role of ACST in patients with poorly responsive or primary refractory disease was not known. Despite the introduction of novel, more targeted agents in the induction and maintenance phases, such as proteasome inhibitors (bortezomib was first in class) & Immunomodulatory drugs (IMIDs; thalidomide was first in class) with associated improved outcomes(26-28), for most patients, a cure remains elusive and the disease will eventually relapse. Because of recent advances, many options to manage disease relapse exist, but no standard of care treatment has been clearly defined. Thalidomide, bortezomib, and lenalidomide form the mainstay of treatment in combination with steroids and conventional chemotherapy.

The use of a second ASCT at relapse (salvage or sASCT) after a prior ASCT, is an appealing option because of the potential for long-term disease control and the reasonably good tolerability of the procedure. However, the evidence base for such a clinical intervention remained scant, non-systematic and most often single-centre analyses (29) though

there is a suggestion of an important role for sASCT though no prospective randomised evidence exists, especially not in the era of novel, targeted anti-MM agents.

2.2 Publications.

Three publications are important in the developing theme of unmet need for sASCT therapy in MM. The first publication, examines the role of ASCT as salvage therapy for patients with poorly performing disease, including primary refractory disease, and how ASCT may overcome this adversity. Based on a registry retrospective study, this publication highlights the salvage capability of ASCT in the face of poorly responsive disease to SoC induction therapy (30). The second publication sought to examine the use of a second ASCT after relapsing from a prior ASCT, here in referred to as a salvage ASCT (sASCT), and attempted to define the clinical utility of sASCT including factors associated with outcomes(31). This registry-based analysis largely reflected patients who received combinational chemotherapy in the era before novel, targeted agents were incorporated in the induction phase for patients with MM undergoing intensive therapy. The third publication represents a limited *real-world* look at the use of sASCT after a bortezomib-containing re-induction therapy in a limited number of centres, to add further to the evidence base for clinical utility of sASCT but in the modern era of novel agents(32).

1. C Parrish, J Apperley, A Bloor, R Pearce, K Kirkland, J Lee, C Craddock, K Wilson & **G Cook**. (2015) On behalf of the British Society of Bone Marrow Transplantation Clinical Trials Committee The Role of High Dose Chemotherapy and Autologous Stem Cell Transplantation in Patients with Multiple Myeloma Refractory to Initial Induction Therapy. *Biology of Bone Marrow Transplantation*. doi 10.1016/j.bbmt.2015.03.026
2. **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
3. TCM Morris*, **G Cook***, M Streetly, P Kettle, M Drake, M Quinn, J Cavet, J Tighe, M Kazmi, J Ashcroft, M Cook, J Snowden, A Olujohungbe, S Marshall, J Conn, H Oakervee, R Popat & J Cavenagh. (2011) Re-transplantation after Bortezomib-based therapy. *British Journal of Haematology* 153(5):666-8

2.3 Discussion.

There was a clear clinical need for sASCT though the evidence base was somewhat lacking and certainly devoid of randomsied controlled trial (RCT) data. Furthermore, there is still a role for sASCT in the modern era of novel, targeted therapies in MM. We found, using *real-world* data, that responses to a bortezomib-based re-induction therapy are comparable to that seen with primary induction therapy, with the majority of patients demonstrating better responses to sASCT compared to their first-line ASCT. This effect post-sASCT, is mostly due to the deeper responses obtained using a combination of novel agent re-induction and sASCT, though the true depth of response, namely MRD negativity as established in first line ASCT, is not known from the limited datasets available in sASCT. The data available from retrospective studies and *real-world* evidence represents a good prognosis group of patients on the basis of their median disease control following their first ASCT. However, the limited evidence does demonstrate that this approach is both feasible and efficacious and underpins the need for a RCT in this area. Such an RCT is the Cancer Research UK National Cancer Research Institute Myeloma X study in patients at first relapse, supported both by the UK Myeloma Forum and the British Society for Blood and Marrow Transplantation Chapter 3 and 4). This study aimed to determine if a sASCT is warranted if a potent re-induction regimen is utilized to maximum response.

Chapter 3

Salvage ASCT utility – Results of the NCRI Myeloma X Relapse (Intensive) Trial

3.1 Introduction

Though limited, the available data for the utility of a sASCT for patients relapsing after a prior ASCT demonstrates a clinical need in MM. However, there is no prospective, randomised controlled trial (RCT) evidence of its safety and efficacy, and certainly not in the era of novel targeted drugs in the treatment pathway of patients with MM. Consequentially, in 2006, on behalf of the UK Myeloma Forum and the British Society of Blood and Marrow Transplantation, I designed the National Cancer Research Institute Myeloma X Relapse (Intensive) trial to compare high dose melphalan plus sASCT with a non-transplant consolidation strategy (NTC; oral cyclophosphamide) in patients with relapsed MM who had previously undergone ASCT in the first-line setting (NCT00747877; https://clinicaltrials.gov/ct2/show/NCT00747877). The choice of cyclophosphamide as post re-induction consolidation for patients in the control group represented an accepted UK SoC practice in the absence of a global SoC in this setting.

The trial schema is illustrated in Figure 3.1. All patients were registered at trial entry and received re-induction therapy with 2-4 cycles of PAD (bortezomib (formerly PS-341), doxorubicin (formerly Adriamycin) and dexamethasone), delivered as previously described(33). The impact of using PAD treatment on the mobilization of peripheral blood stem cells (PBSC) in first line therapy has been demonstrated(34). However, the impact on re-mobilization after a prior ASCT and PAD re-induction was not known, therefore patients recruited into the trial underwent PBSC mobilization and harvesting following PAD treatment (mobilization and harvest was optional in patients who have

sufficient PBSC stored from a previous harvest). Those patients who successfully completed the re-induction stage (in the absence of progressive disease) and mobilization (including those who did not mobilize but had stored PBSC from prior mobilizations) were randomised and assigned one of two treatment strategies: either HD melphalan and sASCT or NTC. No maintenance therapy was delivered and patients were followed for the time-dependent endpoints, illustrated in Table 3.1.

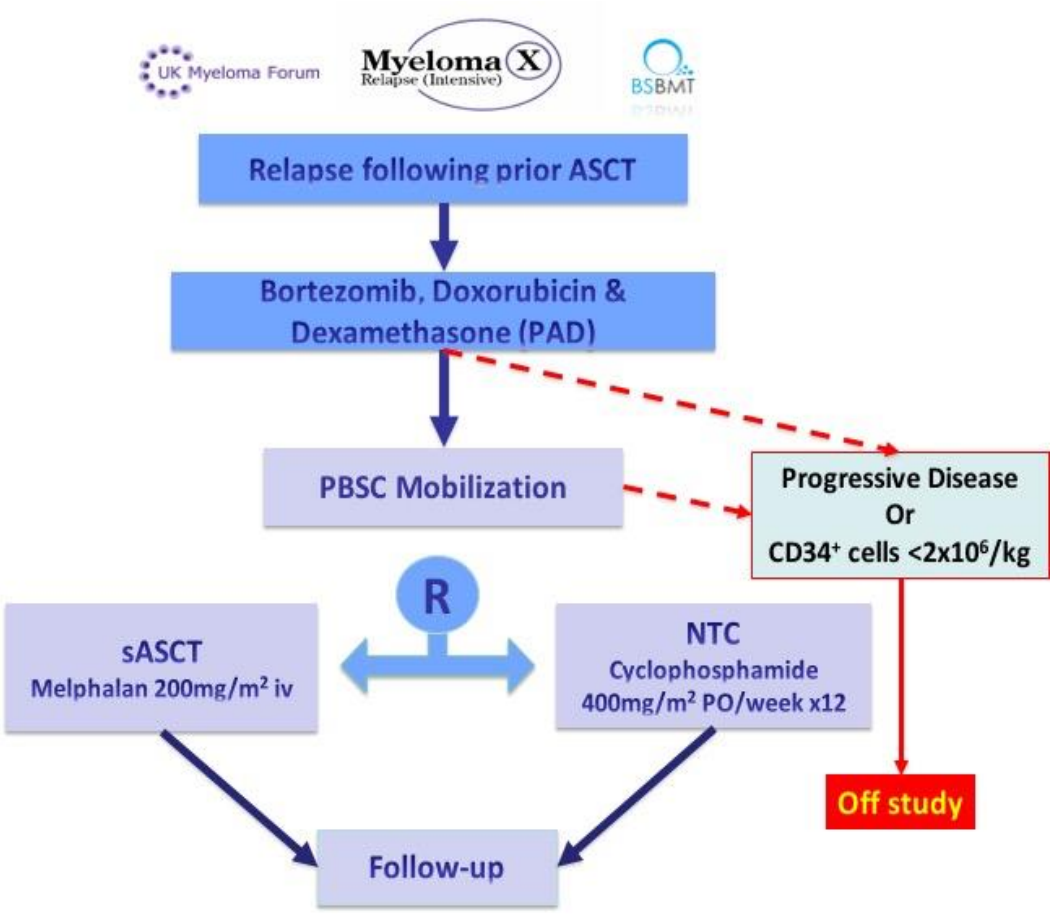

Figure 3.1 NCRI Myeloma X Relapse (Intensive) trial schema

Primary Endpoint	Secondary Endpoints	Exploratory Endpoints
Effect on freedom-from disease progression of a salvage ASCT (ASCT2) compared with non-transplant consolidation (NTC).	**Overall Response Rate (ORR) to PAD, ORR of sASCT versus NTC** **Progression-free survival** **Overall Survival** **Safety & toxicity** **Feasibility of stem cell collection at relapse from a prior ASCT** **Assess whether type of PBSC mobilization & harvest is prognostic of PFS** **Quality of Life (QoL)**	**Effect of randomised treatments on minimal residual disease (MRD)** **Impact of tumour genetic risk on outcomes** **Impact of genetic variants of pain pathways & QoL by outcomes**

Table 3.1 Primary, secondary and exploratory endpoints in the phase III NCRI Myeloma X Relapse (Intensive) trial.

The trial opened in April 2008, recruiting from 60 centres in the United Kingdom and Northern Ireland. There were delays in opening the trial at participating sites, some sites taking up to 12 months to gain appropriate approval to start recruiting (Figure 3.2). The recruitment of suitable patients was an issue such that recruitment fell below expected targets (Figure 3.3) and gaining a clear understanding of the reasons for faltering recruitment was key in the early stages of delivery of the trial. Furthermore, a higher than predicted proportion of patients recruited into the trial did not proceed through the randomization (Figure 3.4), the reasons for failing to be randomised are illustrated in Figure 3.5.

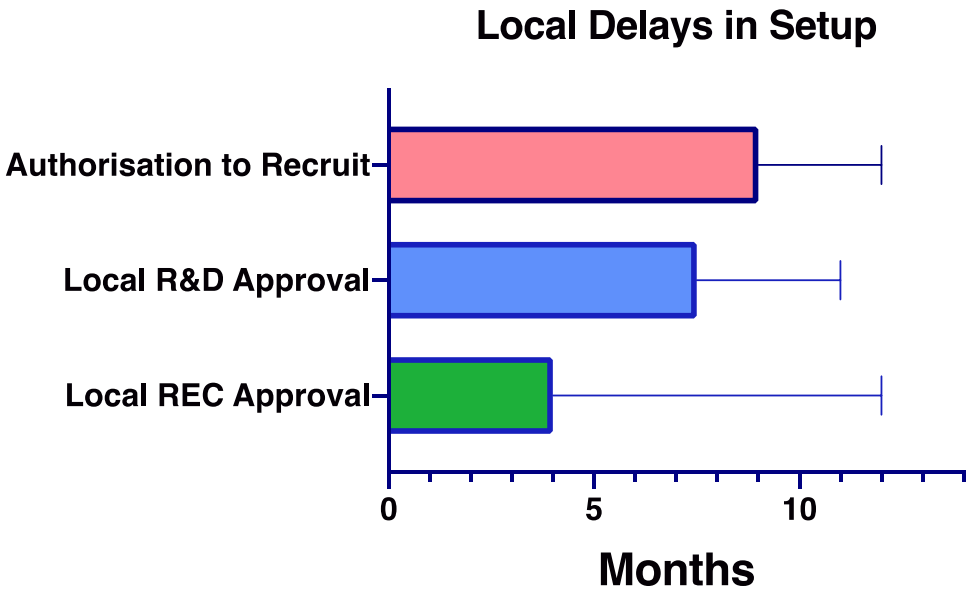

Figure 3.2 Delays in local trial activation for NCRI Myeloma X Relapse (Intensive) Trial

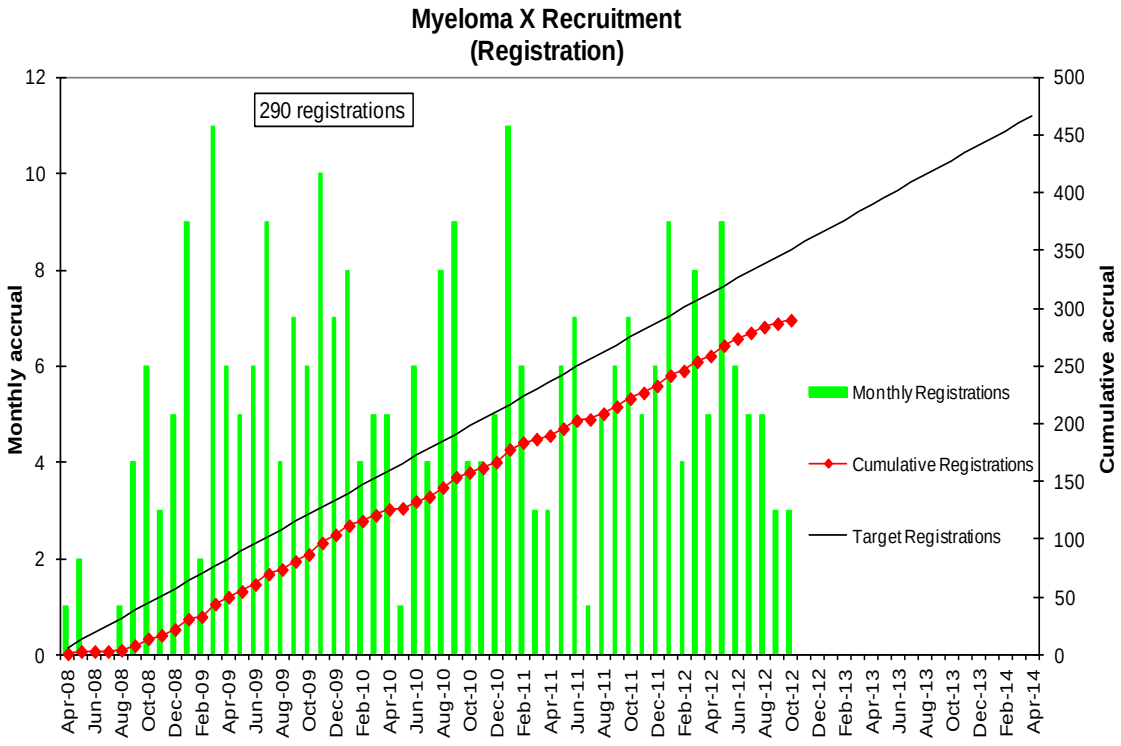

Figure 3.3 NCRI Myeloma X Relapse (Intensive) trial registrations up to 23/10/2012.

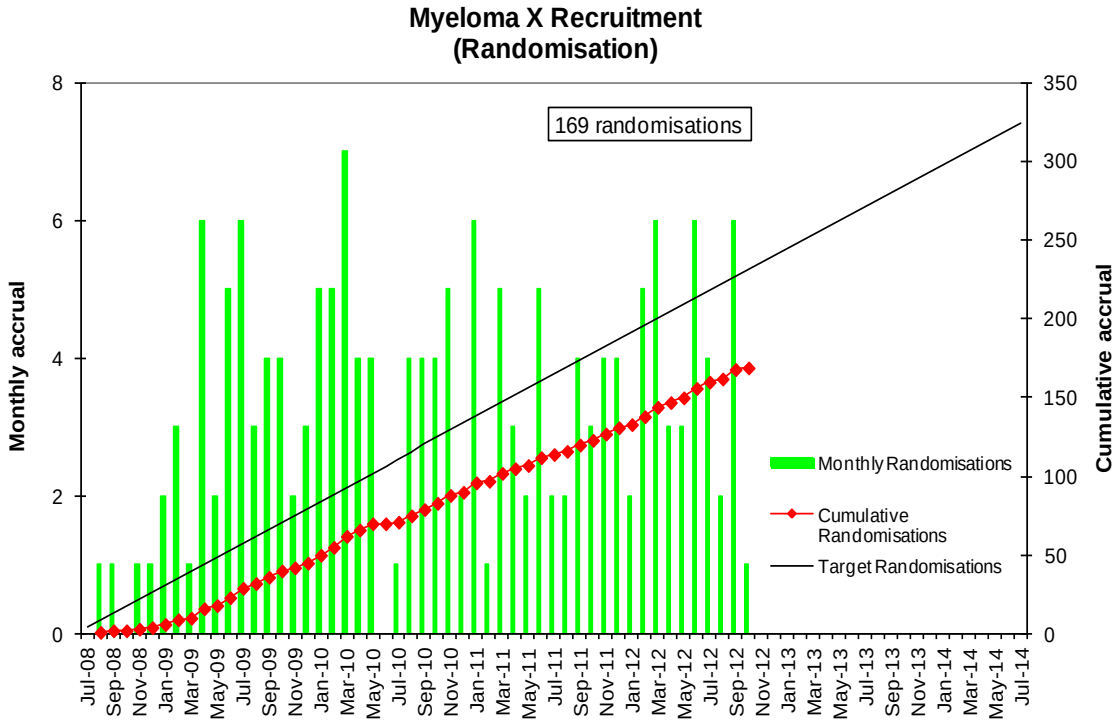

Figure 3.4 NCRI Myeloma X Relapse (Intensive) trial randomisations up to 23/10/2012

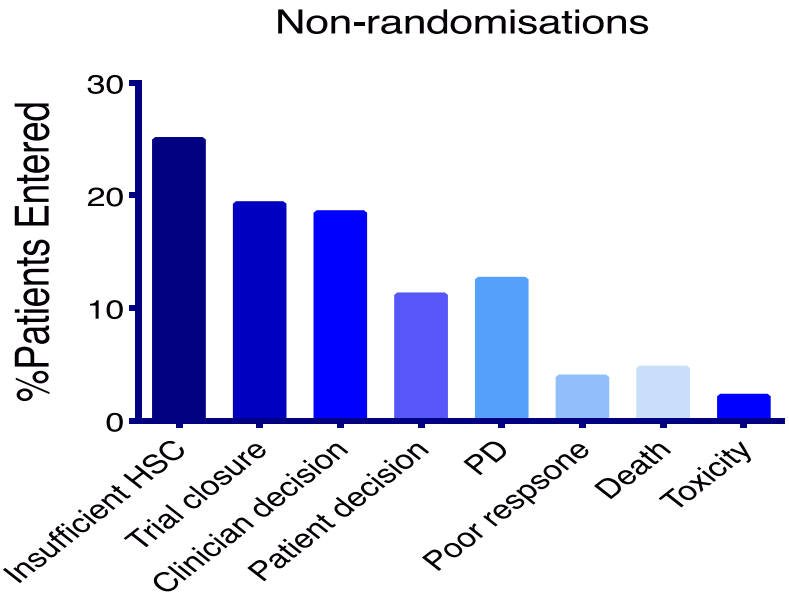

Figure 3.5 Reasons for failing to proceed through randomisation in the NCRI Myeloma X Relapse (Intensive) trial

The trial closed to recruitment in November, 2012, after an interim analysis of the primary endpoint was performed at the request of the independent Medical Research Council Leukaemia Data Monitoring and Ethics Committee (DMEC), showed that the prespecified boundary (defined as a guideline as $p<0.001$) representing "overwhelming evidence" had been met. The DMEC reviewed all the information that they requested about statistical significance and the estimated treatment effects to come to a decision, and on the basis of the DMEC review, the chair of the Leukaemia Trials Steering Committee recommended that the trial be closed and the results unmasked. The cutoff date for the final analysis was July 9, 2013, when the database was locked for final analysis.

3.2 Publications.

Five publications from the trial establish the clinical utility of sASCT in patients relapsing after a prior ASCT. The first publication examines the reasons and patient attitudes towards sASCT, as a way to trying to understand the slow recruitment into this RCT(35). Using the screening logs from trail-active sites, we discovered that the main reason for patients not being entered was because of clinical ineligibility according to the protocol but who undoubtedly proceeded to sASCT off trial (later a comparison of trial recruitment to *real-world* sASCT data from the BSBMT registry confirmed this).

The second publication represented the first reporting of the primary objective, namely the effect on disease durability of response when consolidation with sASCT is utilised compared with a non-transplant consolidation(36). This publication represents the first ever RCT evidence for the role of sASCT in treating relapsed MM. The third publication highlighted the impact of sASCT on the survivorship (OS) of patients with relapsed MM,

as well as providing an update on the time-dependent disease control from the randomised treatments, namely time-to-progression (TTP) and progression-free survival (PFS)(37).

The fourth publication provided the first evidence that PBSC could be mobilised in patient who had previously undergone a ASCT in first line, subsequently relapsing(38). This important evidence is key for the logistical support of patients who may be suitable for sASCT both in planning their PBSC mobilisation in first line and for those with insufficient PBSC to support a sASCT highlighting they can potentially re-mobilize after a prior ASCT and thus impact on the utility of sASCT in the *real-world* setting.

A fifth manuscript highlights the impact of sASCT versus NTC on the attainment of a minimal residual disease negative state, and the impact this has on outcomes (De Tute R, Cook G, et al; under submission review by *Bone Marrow Transplantation*). As has been previously highlighted, attainment of a MRD negative sate, as defined by multi-parameter flow cytometry is associated with improved disease durability of response and overall survival in the front line setting(24, 25). Both at the time of the NCRI Myeloma (Intensive) Trial and since, there has been next to no evidence published about the impact on outcomes of attainment of a MRD negative state in the relapse setting and sASCT, though once again the *treatment agnostic* nature of MRD negativity is highlighted in this manuscript.

1. TCM Morris, C Williams, S Bell, M Fletcher, A Szubert, J Cavenagh, J Snowden, J Ashcroft, K Yong, J Cavet, J Brown & **G Cook**. (2013) Patient perceptions of second transplants in myeloma: impact on recruitment in the BSBMT/UKMF Myeloma X Relapse (Intensive) Trial. *British Journal of Haematology*, 163, 4, 541-3.
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) A Second Autologous Stem Cell Transplant Induces Superior Durability of Response following Bortezomib-containing Re-induction Therapy for Relapsed Multiple Myeloma (MM): Final Results from the BSBMT/UKMF Myeloma X (Intensive) Trial. *The Lancet Oncology,* Vol. 15, No. 8, p874–885.
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) The impact of salvage autologous stem cell transplantation on overall survival in patients with relapsed multiple myeloma: Final results from the BSBMT/UKMF Myeloma X Relapse (Intensive) randomised open-label phase 3 trial. *The Lancet Haematology*, 3, 7; e340–e351
4. 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* doi: 10.1016/j.bbmt.2016.01.016

3.3 Discussion.

The management of relapsed MM after a previous ASCT has evolved over the past two decades with the advent of strategies containing new, more biologically targeted agents as opposed to chemotherapy. Before this period, and concurrent with such developments, the use of sASCT in the first relapse setting had a role in routine clinical practice. By 2006 (the start of the NCRI Myeloma X Trial) there were only seven published studies of the use of sASCT which by 2013 (the end of the NCRI Myeloma X trial) had risen by a further 12 studies. On systematic review of these publications, the evidence to support sASCT was based on retrospective registry or single-centre studies only, mainly without the incorporation of new agents in the re-induction phase and a clear absence of RCT-based evidence. The NCRI Myeloma X (Intensive) trial demonstrated that high-dose melphalan plus sASCT administered at first relapse significantly prolongs time-to-progression compared with conventional NTC, after the use of a re-induction regimen containing a new agent (bortezomib). Furthermore, in subsequent analysis, we demonstrated that this had a significant impact on overall survival. The results provided the necessary prospective evidence not only substantiating the previous retrospective studies in an up-to-date clinical treatment scenario, but also showing the clinical utility of sASCT in MM at first relapse which can aid the decision-making process for both physicians and patients with MM at first relapse.

Once again, the treatment agnostic nature of MRD negativity is demonstrated. That is, both sASCT and NTC could induce MRD negativity which is associated with superior outcomes, but the former (sASCT) as opposed to the latter (NTC) can induce MRD negativity in a higher proportion of patients. Such is the clinical utility of sASCT.

Chapter 4

Salvage ASCT – Utility in molecular high risk disease and patient impact

4.1 Introduction

Multiple myeloma (MM) is a heterogenous clinical-pathological disease and how it affects a particular individual patient is variable, under-pinned by the adage “one size doesn't not fit all” consequential to both patient- and disease-related factors. In terms of disease factors, in addition to tumour burden and the impact on end-organ function (as described in Chapter 1), there is a clear tumour genomic spectrum which has been recognized as a prognosis-defining criteria for several decades, especially in newly diagnosed patients, utilizing interphase fluorescence *in situ* hybridization (iFISH)(39). In particular, mutation and deletions of the tumour-suppressor gene, *TP53,* on chromosome 17 (17p deletion) as well as balanced translocations involving *IGH* on Ch14q32, particularly t(4,14), are associated with a poor prognosis, while hyperdiploidy is associated with improved outcomes (40, 41). Emergence of poor prognosis aberrations is postulated as one mechanism of resistant relapse; patients with multiple poor prognosis aberrations are described as having “ultra-high-risk” or “double-hit” disease, and have an even higher risk of progression and poor survival than those defined as “high-risk” (one poor prognosis aberration) (42). However, the datasets are largely derived from frontline, newly diagnosed patients. In particular, data relating to the impact of clonal genomic evolution (changes from diagnostic genomic landscape to first relapse) on outcomes following sASCT is lacking.

The impact of improved disease control and durability of control results in an increasing proportion of patients living longer with MM. However many remain symptomatic as a consequence of disease- and treatment-related symptoms as well as comorbidity interactions even in remission. A cumulative burden of symptoms and treatment adverse effects (including ASCT), including various forms of pain perception, all affect health-related quality of life (QoL) (43). Studies have highlighted patient-reported outcomes (PROs) measuring the impact of both novel agents and ASCT on QoL in patients with MM (44). However, no data exists on the impact of sASCT compared with nontransplantation consolidation (NTC) with oral cyclophosphamide on PROs and related QoL.

4.2 Publications.

Three publications from the trial examine the utility of sASCT in high risk disease and the impact on quality of life. The first publication (45) examined the effect of molecular high risk disease on time-to-progression (TTP) and OS. We found that the presence of any single high-risk lesion had a negative impact on the durability of response with a *MYC* rearrangement having a particular detrimental impact on OS. There is evidence that the benefit of a sASCT in first relapse after a prior ASCT is reduced in molecular high-risk patients, highlighting the need for either a more targeted study in this group of patients or exploring the role for novel agent and ASCT combinations alongside maintenance post-sASCT.

The second publication examines the impact of sASCT on PROs and QoL at first relapse after a prior ASCT and reinduction chemotherapy. Given that we demonstrated sASCT to be superior to NTC in terms of TTP and OS, there was a need to define the sASCT-

related toxicity in the short and long term QoL and evaluate the association of QoL with subsequent clinical outcomes and to identify patient subgroups that may gain the most QoL benefit from sASCT. We defined that patients with sASCT demonstrated a comparative reduction in QoL and greater impact of treatment adverse effects lasting for 6 months and up to 2 years for pain, after which they reported better outcomes (47), with patients who experienced lower adverse effects after sASCT having longer TTP and OS.

The third publication highlights a further inter-patient variable when considering first relapse salvage therapy, namely an inherited genetic variance in relation to systematic assessment of PRO outcomes at key points of treatment through exploring single nucleotide polymorphism (SNP) genotyping (46). We demonstrated that a non-coding SNP was associated with several relevant pain and health-related QoL scores at 100 days after randomized therapy but these effects were not modified by treatment arm and were no longer significant at 6 months. Thus there was not a significant burden of evidence to support the potential for adoption towards personalized treatment strategies, though trend interpretation did persist. This was an exploratory study which did support associations between subjective parameters in MM with SNPs previously identified in genome-wide association studies of pain.

1. **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, 450-67 doi/10.1111/bjh.15782
2. SH Ahmedzai, JA Snowden, AJ Ashcroft, DA Cairns, C Williams, A Hockaday, JD Cavenagh, C Parrish, JM Brown, TCM Morris & **G Cook** on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. (2019) The effect of salvage autologous stem-cell transplantation on patient-reported outcomes in relapsed multiple myeloma: results from NCRI Myeloma X Relapse [Intensive]): randomised phase 3 trial. *Journal of Clinical Oncology 37, 19, 1617-28* DOI: 10.1200/JCO.18.01006.
3. J Snowden, S Ahmedzai, A Cox, DA Cairns, AJ Ashcroft, C Williams, J Cavenagh, A Hockaday, J Brown, I Brock, TCM Morris & **G Cook**. (2022) Association of Genetic Variants with Patient Reported Quality of Life and Pain Experience in patients in the UK NCRI Myeloma X Relapse [Intensive]) trial; an exploratory study. *Bone Marrow Transplantation* doi: 10.1038/s41409-022-01738-y

4.3 Discussion.

The sub-group analyses presented in this chapter provide the first evidence of the impact of disease- (clonal genomic landscapes) and patient- (PROs and inheritable somatic genetic variations) related features in the setting of sASCT. The publications highlight that the gains in TTP, PFS and OS observed from Myeloma X (Intensive) trial are robust, confirmed by the later follow-up. This remains the first, and only, randomized evidence for sASCT ahead of the reporting of the German-speaking Myeloma Multi-centre Group (GMMG) ReLApsE trial(48). This study used an IMiD-based control group, which is widely considered to be superior to the NTC used in Myeloma X. The genomic landscape with relapsing disease can vary from that seen at diagnosis with both loss and gain of adverse iFISH-detected prognostic factors and confirm that the gain of such factors does affect prognosis in patients at first relapse. Whilst the majority of patients retain their cytogenetic findings from diagnosis, some patients develop adverse cytogenetic characteristics while others lose theirs (or they are at least reduced to undetectable levels), which has never been reported until Myeloma X trial. This highlights sub-clonal selection through the use of novel agents and prior ASCT. The Myeloma X data confirm the findings of the Intergroupe Francophone du Myelome (IFM) study (49), but not by the longitudinal German-speaking Myeloma Multi-centre Group (GMMG) study, where acquisition of additional (adverse) cytogenetic findings (seen in approximately one in eight of our patients) was well recognised, but where loss of poor prognostic findings (seen in one in 20 of Myeloma X patients) was not frequently described (50).

It has been shown that MM harboring *MYC* abnormalities in general have advanced tumor features and adverse outcomes even with low proliferation (51). Trisomy 8 also

contributes to unfavorable outcomes in MM, the chromosomal localization of the *MYC* gene. Unfortunately, data on *MYC* rearrangements were not available for patients at diagnosis and evidence for inclusion of 1q21 gain was lacking when Myeloma X was designed. In our dataset, *MYC* rearrangements were particularly associated with poorer outcomes from sASCT. The outcomes associated with genetic high risk disease in Myeloma X highlight that the current clinical interventions do not circumvent this adversity, highlighting the need for newer targeted strategies for this sub-group of patients.

The impact of PROs on outcomes in relapse MM has only recently been described but the relationship has mainly been in the setting of novel triplet agent combinations where only 60% were at first relapse (52, 53). The novel agent combinations demonstrate improved PFS not to the detriment of QoL. In a similar way, we demonstrate the disease response durability and survivorship improvements did not come at the expense of QoL. It is important to note the limitations of the PRO measurements in Myeloma X. As the trial was not blinded (not feasible given the randomized interventions), this may have had an unpredicted impact on subjective end points such as pain, treatment adverse effects, and QoL are of interest. Furthermore, the attrition rate reported in the trial may also have been a possibly source of bias if they occur differentially in allocated treatment arms. It has previously been shown that attrition can overestimate QoL scores though this can be consistent over time and between allocated treatment arms (54). The benefits of sASCT should be considered alongside the relatively short-term negative effects on QoL and pain when making patient treatment decisions and further support the use of sASCT.

The exploratory results from the inheritable gene analysis relating to PROs in Myeloma X highlights this is as an area for further research in MM and potentially other cancers associated with pain. The ultimate benefit of this and subsequent research will be to identify patients who are more at risk of developing pain and other symptoms, and this would enable more detailed discussions between clinician and patient about the use of intensive therapies such as sASCT, in order to improve the patient experience as well as enhance survival. Further exploration of whole genome sequencing to highlight pathways important in appreciation of treatment emergent symptoms may result in further therapeutic benefits in personalized care.

Chapter 5

Salvage ASCT – Clinical *real-world* impact

5.1 Introduction

Randomized clinical trials (RCTs) are the "gold standard" for evaluating the safety and efficacy of new therapeutic agents or novel combinations. However the stipulation of necessary strict inclusion and exclusion criteria results in the trial populations often not being representative of the patient populations encountered in clinical practice – the *impact evidence gap*. Significant improvements in outcomes across the expanding publication landscape in MM is encouraging. However, these therapeutic strategies may have limitations in the *real-world* setting(55). This in part may relate to toxicity burden, patient treatment burden, and other factors including cost, that are not evident in the selected population that forms the trial dataset. Consequently, despite improvements in efficacy in the rigorously controlled clinical trials setting, the same results are not always achieved in *real-world* practice. Furthermore, multiple aspects, including patient-, disease- and treatment-related factors, can influence clinical trial outcomes and lead to differences between studies that may confound direct comparisons between data and the expected results in the *real-world* setting (56).

In 2014, the Research Excellence Framework (REF) incorporated the use of impact case studies to highlight the impact of academic research on the wider society (https://www.ukri.org/about-us/research-england/research-excellence/ref-impact/).

Impact was defined as '*an effect on, change or benefit to the economy, society, culture, public policy or services, health, the environment or quality of life, beyond academia*'. In the context of the work presented in this thesis, the impact was generated around

incorporation into clinical guidelines (national and international), clinical adoption in to *real-world* practice and an examination of *real-world* outcomes.

5.2 Publications.

The published work presented in chapters 3 and 4 forms the basis of the trial-derived evidence for clinical practice adoption and change in patient opportunities. The UK Myeloma Forum (now called the UK Myeloma Society; UKMS), represents the clinical and academic myeloma community and continually reports best practice guidelines based on updated publications and evidence (https://ukmyelomasociety.org.uk/). In 2014, the UKMF produced an update to the 2011 guidelines, which incorporated the use of sASCT in first relapse for selected patients with MM (57). The UKMS, in conjunction with the British Society of Haematology Guidelines Group, is currently preparing for publication (in 2023) an update of the relapse MM treatment guidance and sACST remains as a suggested therapy for first relapse. In 2016, the National Institute for Clinical Excellence (NICE) produced a MM diagnosis and treatment guideline (NG35) which highlighted the utility of sASCT in first relapse and recommended sASCT for selected patients (www.nice.org.uk/guidance/ng35). The British Society for Blood and Marrow Transplantation and Cellular Therapy (BSBMTCT) have recently revised their stem cell transplantation indications table, published on line in 2023 highlighting sASCT as a standard of care in first relapse, consequential to the publication of the NCRI Myeloma X (Intensive) trial result (https://bsbmtct.org/bsbmtct-adult-and-paediatric-indications-available/)

Four publications selected for this chapter highlight the adoption of the results of the NCRI Myeloma X (Intensive) trial into international clinical guidelines. The first

publication was the output from a American Society of Blood and Marrow Transplantation (ASBMT), European Society of Blood and Marrow Transplantation (EBMT), Blood and Marrow Transplant Clinical Trials Network and International Myeloma Working Group (IMWG) consensus conference on salvage hematopoietic cell transplantation in patients with relapsed MM, held in Minneapolis, USA(16). I wrote the section on prospective trials of sASCT, with the only suitable evidence being the NCRI Myeloma X (Intensive) trial. The second and third publications highlight the acceptance of sASCT in relapse MM guidelines produced by the IMWG (58) and European Haematology Society (EHA/ESMO)(59); I wrote the section on sASCT in both these guidelines. The fourth publication is a consensus guideline generated through the American Society of Transplantation and Cellular Therapy (formerly ASBMT) where I wrote the section on sASCT, and represents an more up-to-date clinical guideline being published in 2022(60).

1. S Giralt, L Garderet, B Durie, **G Cook**, G Gahrton, B Bruno, P Hari, H Lokhorst, P McCarthy, A Krishnan, P Sonneveld, H Goldschmidt, S Jagannath, B Barlogie, M Mateos, P Gimsing, O Sezer, J Mikhael, L Jin, M Dimopoulos, A Mazumder, A Palumbo, R Abonour, K Anderson, M Attal, J Blade, J Bird, M Cavo, R Comenzo, J de la Rubia, H Einsele, R Garcia Sanz, J Hillengass, S Holstein, H Johnsen, D Joshua, G Koehne, S Kumar, R Kyle, X Leleu, S Lonial, H Ludwig, H Nahi, A Nooka, R Orlowski, V Rajkumar, A Reiman, P Richardson, E Rivas, J San Miguel, I Turreson, S Usmani, D Vesole, W Bensinger, M Qazilbash, Y Efebera, M Mohty, C Gasparreto, J Gajewski, C LeMaistre, C Bredeson, P Moreau, M Pasquini, N Kroeger, & E Stadtmauer. (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. *Biol Bone Marrow Transplantation* 21(12):2039-51 doi: 0.1016/j.bbmt.2015.09.016.

2. P Moreau, SK Kumar, J San Miguel, F Davies, E Zamagni, N Bahlis, H Ludwig, J Mikhael, E Terpos, F Schjesvold, T Martin, K Yong, BGM Durie, T Facon, A Jurczyszyn, S Sidana, N Raje, N van de Donk, S Lonial, M Cavo, SY Kristinsson, S Lentzsch, R Hajek, KC Anderson, C Joao, H Einsele, P Sonneveld, M Engelhardt, R Fonseca, A Vangsted, K Weisel, R Baz, V Hungria, JG Berdeja, FL da Costa, A Maiolino, A Waage, D Vesole, E Ocio, H Quach, C Driessen, J Bladé, X Leleu, E Riva, N Abilgaard, L Bergsagel, L Hou, W Joo Chng, U-H Mellqvist, D Dytfeld, J-L Harousseau, H Goldschmidt, J Laubach, N Munshi, F Gay, M Beksac, LJ Costa, M Kaiser, P Hari, M Boccadoro, SZ Usmani, S Zweegman, S Holstein, O Sezer, S Harrison, H Nahi, **G Cook**, M-V Mateos, S.V Rajkumar, MA Dimopoulos & PG Richardson. (2021) International Myeloma Working Group (IMWG) recommendations for the treatment of relapsed and refractory multiple myeloma. *Lancet Oncology*, 22(3):e105-e118 01
3. MA Dimopoulos, P Moreau, E Terpos, MV Mateos, S Zweegman, **G Cook**, M Delforge, R Hajek, F Schjesvold, M Cavo, H Goldschmidt, T Facon, H Einsele, M Boccadoro, J San-Miguel, P Sonneveld & U Mey, on behalf of the EHA Board and the ESMO Guidelines Committee. (2021) Multiple Myeloma: EHA-ESMO Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up *Annals of Oncology*. doi.org/10.1016/j.annonc.2020.11.014

4. B Dhakal, N Shah, A Kansagra, A Kumar, S Lonial, Al Garfall, A Cowan, B Sharma Poudyal, C Costello, F Gay, **G Cook**, H Quach, H Einsele, J Schriber, J Hou, L Costa, M Aljurf, M Chaudhry, M Beksac, M Prince, M Mohty, M Janakiram, N Callander, N Biran, P Malhotra, P Rodriguez Otero, P Moreau, R Abonour, R Iftikhar, R Silberman, S Mailankody, T Gregory, Y Lin, P Carpenter, M Hamadani, S Usmani & S Kumar. (2022) ASTCT Clinical Practice recommendations for transplant and cellular therapies in multiple myeloma. *Transplantation and Cellular Therapy* doi: /10.1016/j.jtct.2022.03.019

To define true impact, demonstrating a change in clinical practice as a consequence of published guidelines is needed. *Real-world* registry-based data can offer a view on changing clinical practice trends. In the pre-trial era (<2006), the annual rate of sASCT in relapsed MM was 60-69 transplants p.a. (source BSBMTCT Data Registry, 2020; Appendix 1). Following the launch and promotion of the NCRI Myeloma X (Intensive) trial, the annual rate of sASCT rose by 194% to 200 sASCT p.a. After the closure of the NCRI Myeloma X (Intensive) Trial, in association with presenting the results at national/international conferences and publishing the manuscripts included in chapter 3, there was a further increase of 46.5% in the annual rate of sASCT to 293 p.a., representing an overall increase of 282% over pre-trial launch annual rates of sASCT (Figure 5.1 and Figure 5.2).

Defining the impact on survivorship in the *real-world* setting of sASCT is very difficult given the multi-modal, multi-line therapy strategy in MM, in conjunction with the ever-expanding treatment landscape(9). Examining the BSBMTCT registry data as presented in the annual report, the 1-year and 5-yer OS rates from sASCT are 93% (95%ci 91, 94) and 49% (95%ci 44,54), as illustrated in Figure 5.3 (Appendix 1). An improved OS is seen from <1999 compared >1999 (Figure 5.4), though this is likely to be driven by non-transplant therapies including novel agents. Using data derived from the Office of National Statistics (ONS), 5-year survival data was extracted from the pre-Myeloma X era (<2006) and compared to the post-Myeloma X reporting years (2010-2018), for all patients, then divided into age-related cohorts (Appendix 2). The age ranges of interest are 50-69 and 60-69 year old cohorts who are eligible for a sASCT. There is an improvement in the 5-year OS of 2.3 percentage point in the 50-59 age group and a 4 percentage point increase in the 60-69 age group, though with overlapping confidence

intervals this is not significant. This is the effect of several evolutions in clinical care but does include the impact of sASCT, and not related to the impact of the (very) recently adopted monoclonal antibody therapy (Daratumumab) in routine clinical practice in May 2019. The impact of the NCRI Myeloma X (Intensive) trial in terms of the clinical community perspective is highlighted in 3 testimonials from leaders in the stem cell transplantation field, from both Europe and the USA (Appendices 3, 4 and 5).

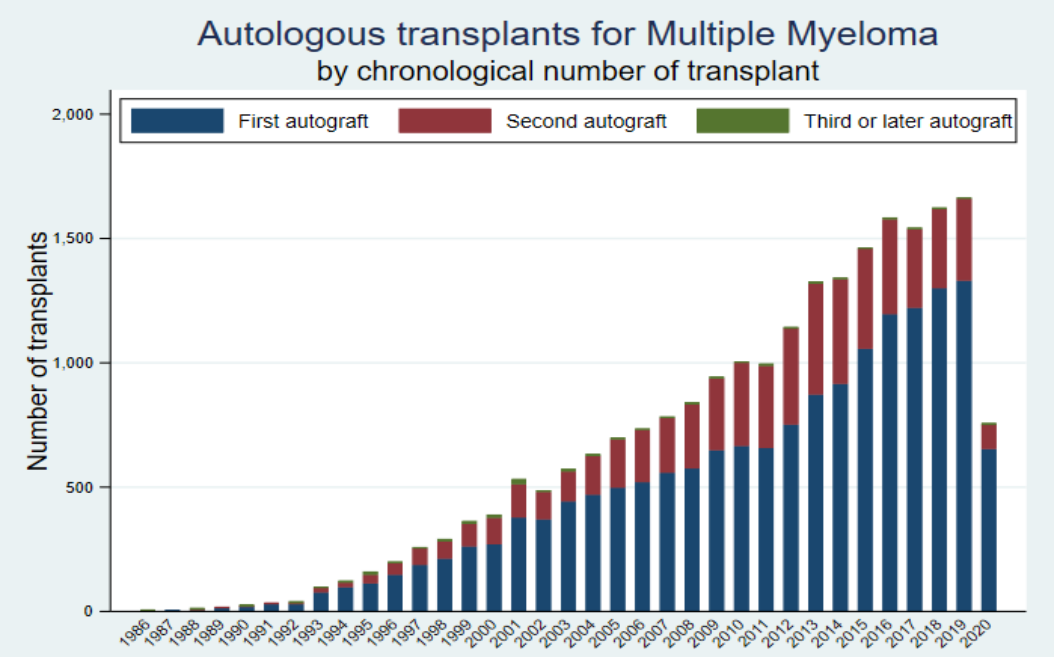

Figure 5.1 BSBMTCT Annual ASCT activity in MM, split according to first ASCT, sASCT (second autograft) and subsequent ASCT (BSBMTCT 2020). Figures represent actual numbers of recorded procedures.

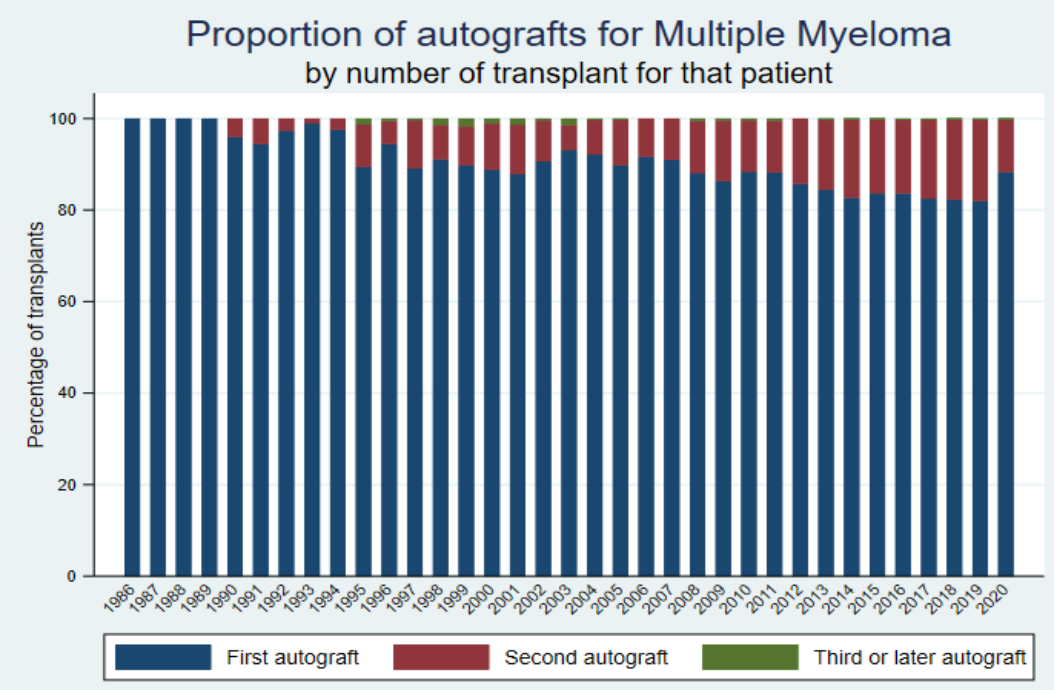

Figure 5.2 BSBMTCT Annual ASCT activity in MM, split according to first ASCT, sASCT (second autograft) and subsequent ASCT (BSBMTCT 2020), by proportionality of annual activity.

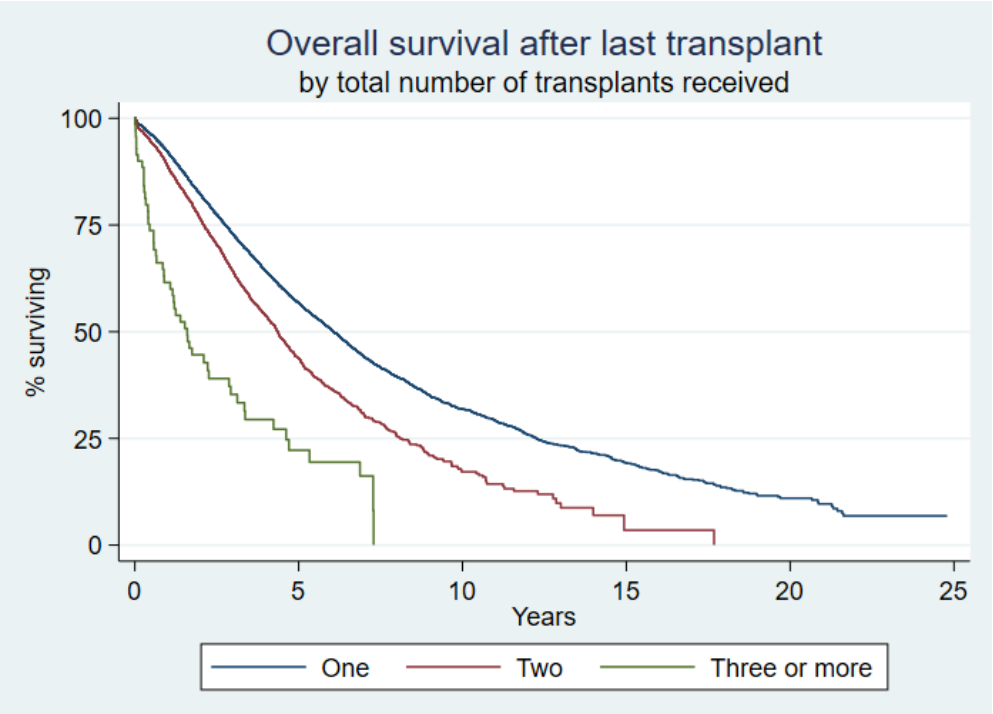

Figure 5.3 BSBMTCT Annual ASCT outcome data in MM, split according to first ASCT, sASCT (second autograft) and subsequent ASCT (BSBMTCT 2020

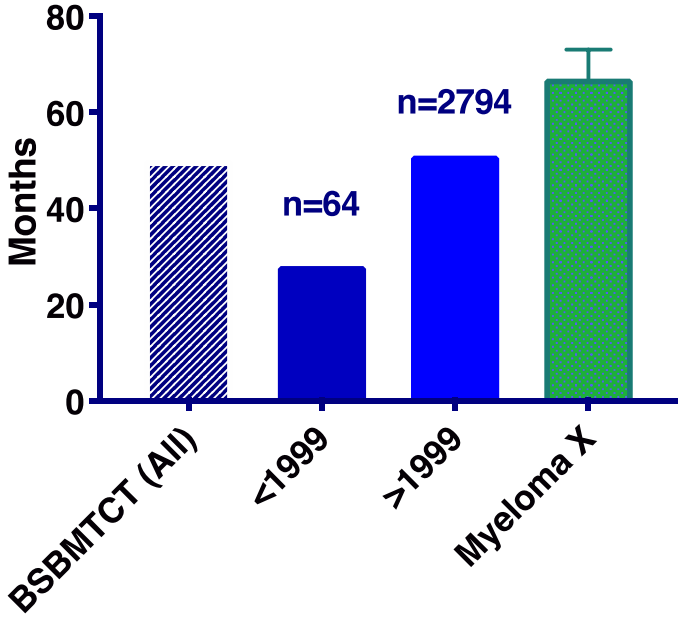

Figure 5.4 BSBMTCT registry and NCRI Myeloma X trial OS data comparison. BSBMTCT Annual Report-derived outcome data, divided into the pre-novel agent (<1999) and post-novel agent introduction (>1999) eras, compared to the trial reported OS (chapter3).

5.3 Discussion.

The purpose of clinical trial research is to change clinical practice through building an evidence base of safety and efficacy to define an improvement in the standard of care. The adoption of the intervention(s) into *real-world* clinical practice and its subsequent assessment will define the effectiveness of this change. The first step of adoption is being included in clinical guidelines that support clinicians in decision making, thus facilitating use of the intervention. Following publication of the results from the NCRI Myeloma X (Intensive) trial (see chapters 3 and 4), the first and only randomized data of sASCT in relapsed MM until 2021, it was incorporated into several national and international guidelines to help patients and clinicians in decision making. The next step is to measure the level of adoption by the clinical community and given that the

transplant community have a long history of *real-world* stem cell transplant activity recording (BSBMTCT, EBMT and Centre for International Blood and Marrow Transplantation Research), we can see the uplift in sASCT activity consequential to the publication of the trial results and incorporation in clinical guidelines.

In order to provide the evidence of treatment effectiveness (as opposed to clinical trial related efficacy) we need to analyse *real-world* evidence. The main issue of RCTs is that it represents the perfect dataset in the imperfect patient population as compared to *real-world* evidence which represents the imperfect dataset in the perfect patient (61). This results from the necessarily strict inclusion and exclusion criteria in RCTs resulting in trial populations often not representing the patient populations encountered in clinical practice. *Real-world* studies can therefore provide information on the long-term safety and effectiveness of interventions in heterogeneous populations. Therefore, to measure true impact, we need to be able to define what benefits society has gained for the adoption of the intervention derived from clinical trial research in the *real-world* clinical practice. In the case of sASCT and the outputs from the NCRI Myeloma X (Intensive) trial, this becomes difficult to assess, especially with the rapidly advancing treatment landscape in relapsed MM alongside the ever-changing regulatory framework under which clinicians have to work in the UK (NICE and the Cancer Drugs Fund). In this context, *real-world* survival data for sASCT from the BSBMTCT registry was examined, and compared with the trial population. A non-significant difference was noted, which for the reason given above, is not unexpected. However this dataset does not relate the effectiveness of sASCT compared to a non-sASCT strategy. In order to assess this, then interrogation of a *real-world* dataset that allows access to all first relapse treated patient populations is warranted (such as the Haematological Malignancy Research Network;

HMRN https://hmrn.org/) but is beyond the scope of this thesis. At present I am proposing a *real-world* retrospective analysis of BSBMTCT data in the recent era, comparing the use of daratumumab/bortezomib/dexamethasone (DVd) and carfilzomib/lenalidomide/dexamethasone (KRD) to re-induction/sASCT strategies. This study should commence Q1 2024.

A criticism of the NCRI Myeloma X (Intensive) trial that often detracts from the output reporting is the design, namely the control arm of oral cyclophosphamide as non-transplant consolidation (NTC). The trial was designed between 2004 and 2006, when the treatment landscape in MM remained focused on cycle-defined, limited duration exposure (LDE) treatment strategies as opposed to continuous duration exposure (CDE), and the NTC adopted as a control in in the Myeloma X trial represented an acceptable standard of care at the time. As the treatment landscape has evolved, almost all new drug combinations brought into clinical practice since the trial opened have been CDE-based therapies, especially in patients with 1-3 prior lines of therapies including prior ASCT(62). Such therapies include the second generation proteasome inhibitor carfilzomib in the ASPIRE trial (KRD (63)) and the CD38-directed monoclonal antibody daratumumab (daratumumab, lenalidomide and dexamethasone; DRd (64); DVD (65)) which are available in the UK (DRd is currently not approved). As a result of these new CDE therapies, the role of sASCT has been questioned and performing a meta-analysis of these trials with sASCT trials is complicated by the lack of prospective sASCT trials. In this context, the GMMG reported the results from the phase III ReLApsE trial where sASCT was compared to CDE (lenalidomide and dexamethasone; Rd (48)). Even though a multi-variate landmark analyses from the time of sASCT showed superior PFS and OS with sASCT, sASCT did not significantly prolong PFS and OS on an ITT basis against Rd

alone. This trial though similar in design, had several differences to Myeloma X. Firstly, up to 46% of patients enrolled had received a tandem ASCT in first line, so the sASCT represented a third ASCT, unlike in Myeloma X where only single frontline ASCT recipients were included. Secondly, only 71% of patients assigned to receive the sASCT actually received the intervention, as opposed all of patients in the Myeloma X trial. None-the-less the study did start to address the issue of sASCT in the era of CDE therapies and of the potential role of maintenance therapy after a sASCT, an evolution of the UKMRA sASCT clinical trials programme (UKMRA Myeloma XII ACCoRD trial).

Chapter 6

The way forward: UKMRA Myeloma XII

6.1 Introduction

The most appropriate strategy as first relapse management (second-line treatment) has evolved in recent years with an expanding portfolio of novel agents, driving better response rates influencing the durability of response (DuR). A sASCT, as part of relapsed disease management has been shown to prolong the progression-free survival (PFS) and overall survival (OS) following a proteasome inhibitor-containing re-induction regimen, as evidenced by the publications in chapter 3 and 4. The sASCT activity in the UK has risen as a consequence of this trial (chapter 5) and it is now recommended that sASCT be considered for suitable patients by national and international guidelines, updated in 2022. My work in this area to date has identified two clear areas of unmet need. Firstly, although superior to non-ASCT consolidation, both the overall response rates (ORR) and DuR post-sASCT were inferior to those reported in first-line treatment. This has been reported in phase III collaborative studies and national/international transplant registries. Hence, the question remains of how to utilise novel agents to abrogate this effect, aiming to achieve similar ORR and DuR to those seen in first-line treatment. Secondly, in the NCRI Myeloma X (Intensive) study, for patients with evidence of molecular high-risk disease (*IGH*, *TP53* and *MYC* rearrangements), the DuR post-sASCT was compromised, despite obtaining similar ORR of response to those for patients with standard-risk disease(45). Consequential to these defined clinical issues and if the depth of response relates to its durability, then two questions remained to be answered in the setting of sASCT:

- Can augmentation of transplant conditioning regimen improve the depth of response and response durability in the salvage setting after a prior ASCT?
- Can post-ASCT consolidation/maintenance improve the response durability post-ASCT?

To address these questions in a phase III clinical trial setting, I designed the concept for the UKMRA Myeloma XII ACCoRD trial in 2013.

6.2 Publications.

Three publications have been selected to highlight the work revolving around the UKMRA Myeloma XII ACCoRD trial. The first is an editorial I wrote setting out the case for re-examining the conditioning for ASCT, whereby combinational approaches may augment the depth of response translating to DuR improvements, and stating the need for prospective clinical trials in this area(66). Augmenting the conditioning regimen for ASCT in MM has been examined in many trials but to date, none have shown any benefit in efficacy or where such a benefit was evident it was not without an increased in toxicity(67).

The UKMRA Myeloma XII ACCoRD trial opened to recruitment in April 2016 (funded by Cancer Research UK, grant awarded in May 2015). The primary objective of the study was to determine the impact on Depth of Response (DoR: <VGPR vs. ≥VGPR) when salvage ASCT conditioning is augmented by the addition of a proteasome inhibitor (ixazomib), and the influence of a consolidation and maintenance strategy on the Durability of Response (DuR: TTP), as illustrated in Figure 6.1. The second publication included in this chapter is the protocol manuscript.

When I set up the UK Myeloma Research Alliance, one of the founding principles was to included discovery science and translational research in all our trials. The third publication is an example of this ethos, whereby bone marrow samples were utilised in a discovery science project within the University of Leeds (Leeds Institute of Medical Research) that I was involved in(68). Several other projects are on-going relating to trial samples, one of which (the immune landscape in first relapse and the impact of sASCT) will be submitted for presentation at the American Society of Hematology Annual Scientific meeting in 2023.

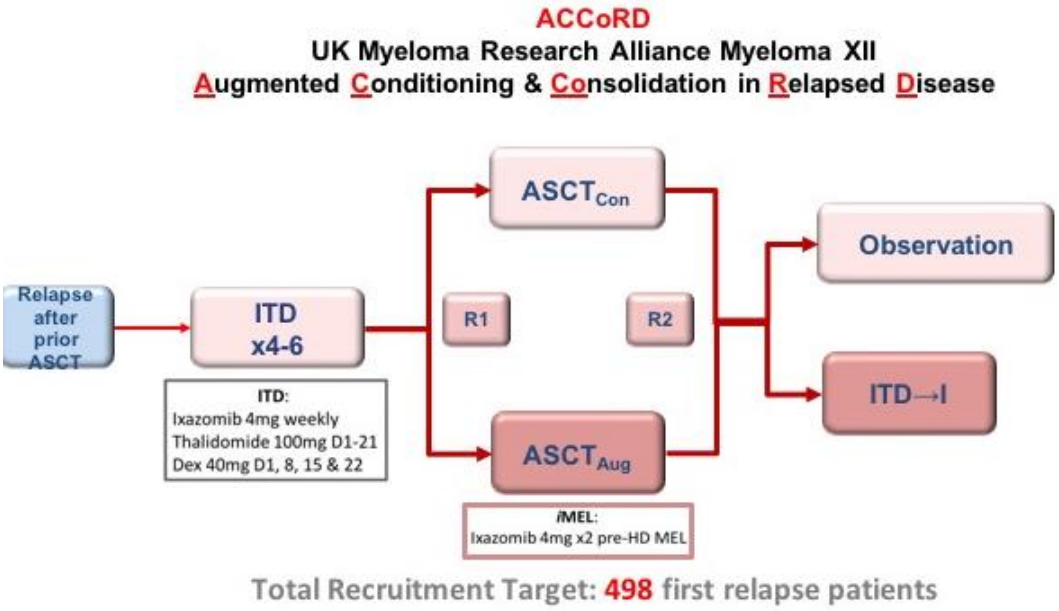

Figure 6.1 UKMRA Myeloma XII ACCoRD Trial schema

1. **G Cook**. (2015) Re-invigorating rather than re-inventing the wheel: Augmenting the impact of salvage autologous stem cell transplantation for multiple myeloma in the era of novel agents. *Bone Marrow Transplantation,* 50(10):1269-70.

2. A Striha, AJ Ashcroft, A Hockaday, DA Cairns, K Boardman, G Jacques, C Williams, J Snowden, J Cavenagh, K Yong, M Drayson, R Owen, M Cook & **G Cook**. (2018) The role of ixazomib as an augmented conditioning therapy in salvage autologous stem cell transplant (ASCT) and as a post-ASCT consolidation and maintenance strategy in patients with relapsed multiple myeloma: the phase III ACCoRd (Myeloma XII) study protocol. *Trials* 19(1):169 doi: 10.1186/s13063-018-2524-8.

3. RJ Brownlie, R Kennedy, M Milanovic, EB Wilson, CF Taylor, D Wang, JR Davies, H Owston, EJ Adams, S Stephenson, R Caeser , DJ Hodson, PV Giannoudis, C Scuoppo, D McGonagle, RM Tooze, GM Doody, **G Cook**, DR Westhead & U Klein. (2023) Cytokine receptor IL27RA is an NF-κB-responsive gene involved in CD38 upregulation in multiple myeloma. *Blood Advances* doi 10.1182/bloodadvances.2022009044

6.3 Discussion.

The UKMRA Myeloma XII ACCoRD trial opened to recruitment in April 2016, with the objectives highlighted in Table 6.1, in 70 sites across the United Kingdom. The trial was besieged by a number of issues requiring extension to the recruitment period as well as the recruitment target. Firstly, at study conception, it was assumed that 30% of registered participants would not reach the first randomization (R1) and 13% of the remaining participants would not reach the second randomisation (equating to 61% of registered participants reaching R2). However, based on the first 12 months of recruited participants, it was observed that 37% of registered participants did not reach R1 and subsequently 30% of the remaining participants did not reach R2 (equating to 50% of registered participants reaching R2). To ensure that the R2 would still recruit the 248 participants required to answer the proposed question, we increased the sample size to 498 participants. The cause of greater than expected R1 failures was due to a greater percentage of participants with progressive disease after re-induction than originally estimated (Estimated: 5% vs Observed: 15%) and 7.5% of patients withdrawn from the trial due to toxicities. The cause of the discrepancy in patients reaching R2 were the result of 5% of R1 participants being ineligible for R2 and 3% of R1 participants being withdrawn from the trial due to toxicities. The trial registration, R1 and R2 graphs are illustrated in Figure 6.2, 6.3 and 6.4.

ACCoRD completed recruitment in June 2022, with database lock for the planned IA in May 2023. 496 patients were recruited, and 206 patients randomised in this comparison. Median age was 62y (range 34, 78) with 36% of patients >65y. The median observed TTP from ASCT1 was 32 months. The proportion of patients with an ASCT1 TTP <18m, 18-24m

and >24m was 11.1%, 16.4% and 72.5%, respectively. 39.5% had standard risk, 16.5% had HR and 5.6% had UHiR disease at trial entry (not performed 38.3%). 61.5% of patients were PI-exposed. I have written an abstract, submitted to the American Society of Hematology Annual Scientific Meeting in 2023 based on the results of R2.

Primary Objective(s)	**Secondary Objectives**
R1 • The impact on Depth of Response (DoR: <VGPR vs. ≥VGPR) when sASCT conditioning is augmented by the addition of a PI **R2** • The influence of a consolidation and maintenance strategy on the Durability of Response (DuR: PFS)	• Overall survival • Time to disease progression • The overall response rate following ixazomib, thalidomide and dexamethasone (ITD) re-induction • Duration of Response (DoR), Time to next treatment (TtNT) & Progression-free survival 2 (PFS2) • $MRD^{negative}$ rate post re-induction, post-ASCT and conversion after ITD consolidation • Engraftment kinetics • Toxicity, safety & Quality of life (QoL)

Table 6.1 Myeloma XII ACCoRD Trial Objectives. R1: randomisaiton 1 between a standard conditioned ASCT versus an augmented (ixazomib and HD melphalan) conditioned ASCT; R2: randomsiaiton 2 between post transplant consolidation (ITD) and maintenance (ixazomib monotherapy) versus observation.

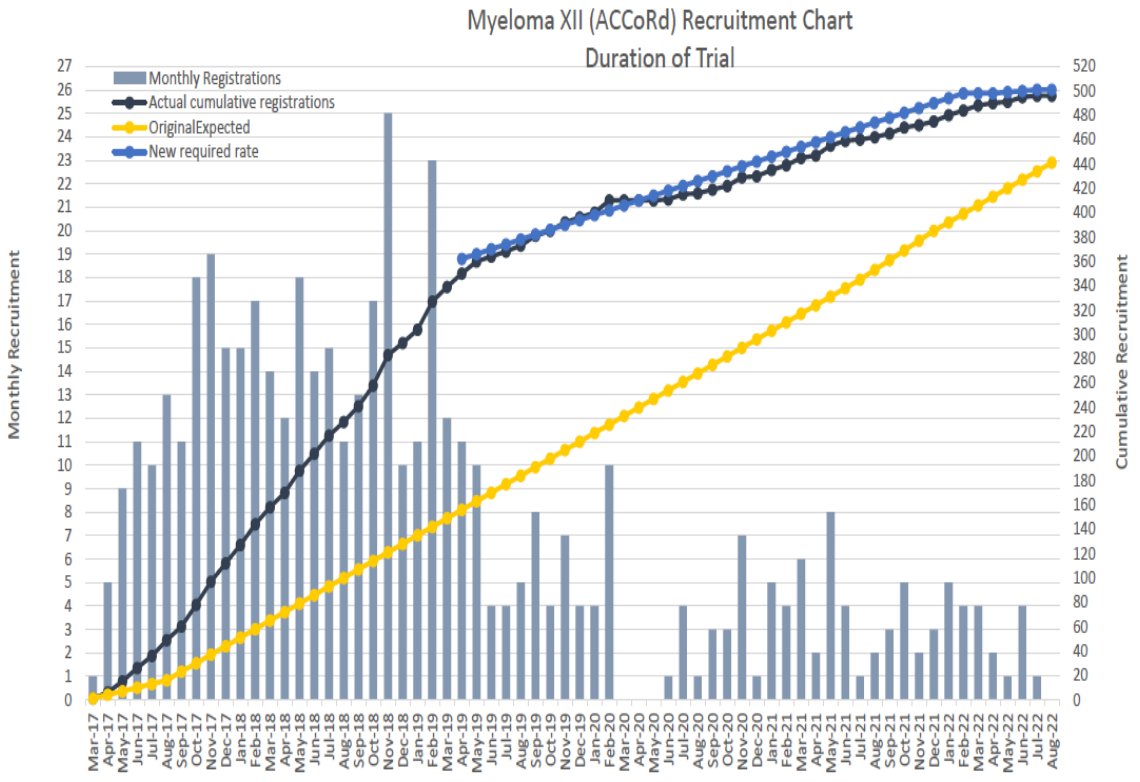

Figure 6.2 UKMRA Myeloma XII ACCoRD Trial recruitment.

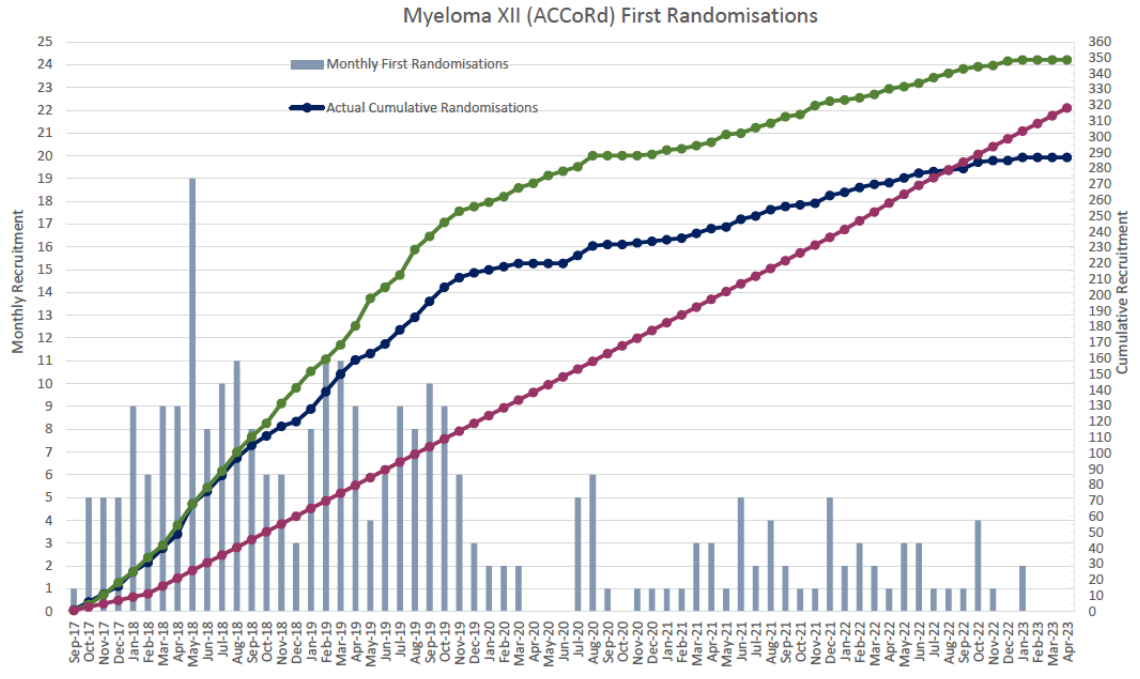

Figure 6.3 UKMRA Myeloma XII ACCoRD Randomisaiton 1 recruitment.

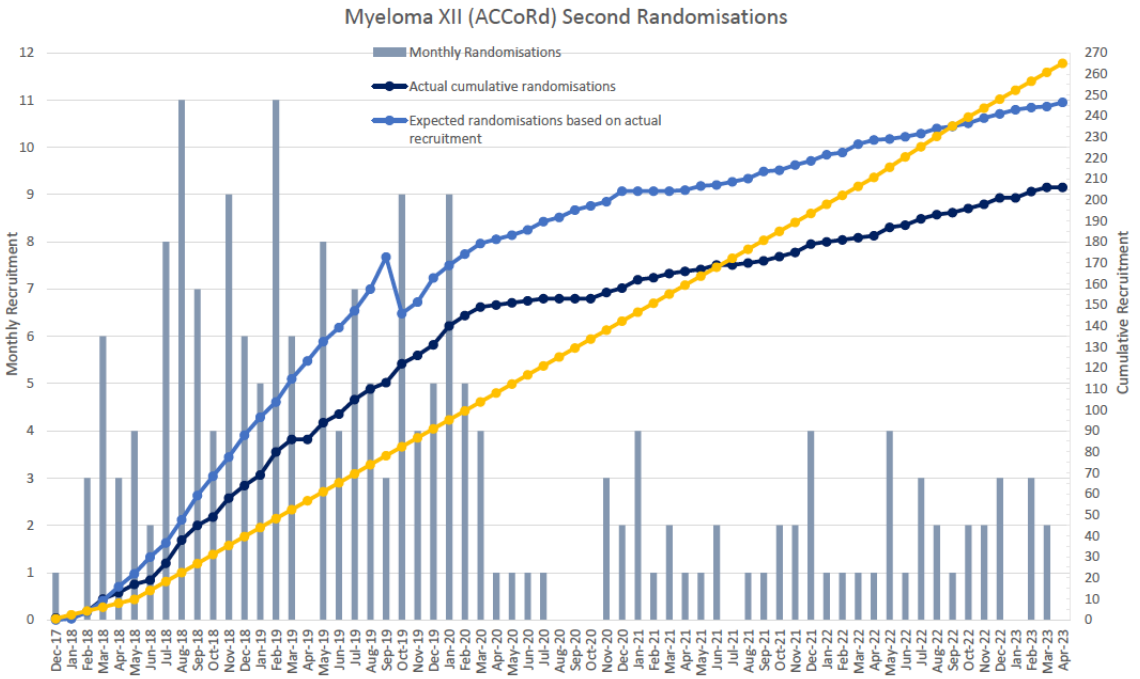

Figure 6.4 UKMRA Myeloma XII ACCoRD Randomisaiton 2 recruitment

The second issue was the changing therapeutic landscape in relapsed myeloma (69). In particular the demonstration of the clinical utility of the CD38-monoclonal antibody, daratumumab, in combination with a proteasome inhibitor- or IMiD-based back-bone (70, 71). In March 2019, a submission to the National Institute of Clinical Excellence (NICE) was made for Daratumumab in combination with bortezomib and dexamethasone (DVd) as an option for treating relapsed multiple myeloma in people who had received 1 previous line of treatment. This was approved for use under the rules of the Cancer Drugs Fund. Consequentially, this impacted the monthly recruitment significantly, as illustrated in Figure 6.5. Subsequently, we conducted a real-world evidence dataset curation, which demonstrated the expected PFS from using DVd in this

setting was less than that reported in the CASTOR trial, and significantly shorter than we reported from the Myeloma X trial, highlighted in chapter 3(72).

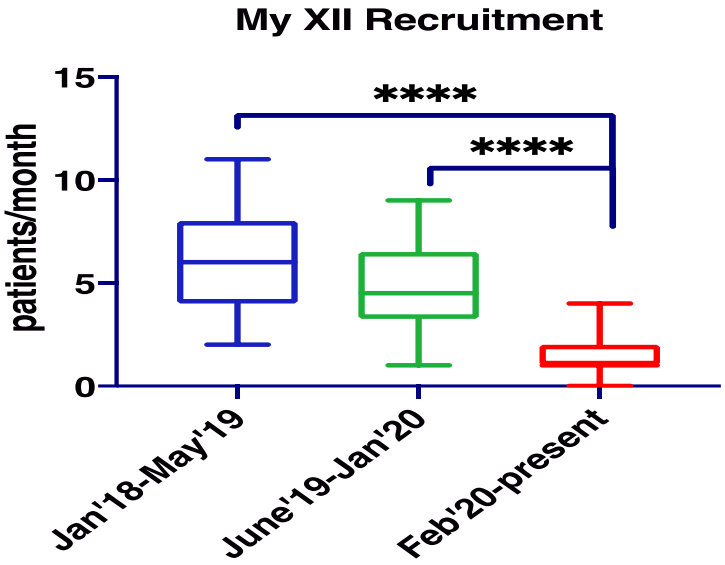

Figure 6.5 Monthly patient recruitment to the UKMRA Myeloma XII ACCoRD trial according to major influential periods. ****p<0.001

Thirdly, and perhaps most importantly, the impact of the COVID-19 pandemic on trial recruitment was very significant (Figure 6.2 and 6.5). Escalating transmission rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causing Coronavirus disease 2019 (COVID-19) rapidly resulted in the evolution of a global pandemic, leading to 48,539,872 known infections, and 1,232,791 deaths in 215 countries by the end of 2020(73). Infection with SARS-CoV-2 has been characterised by differential outcomes, influenced in part by age, sex, ethnicity and co-morbidity profiles but early in the pandemic, blood cancer patients, especially patients with MM, were more likely to experience severe clinical sequelae from infection with poorer outcomes(74, 75). As illustrated in Figure 6.2, recruitment stopped during the first wave, in part by the suspension of delivering ASCT clinical services, in part by the Cancer Drugs Fund COVID-

19 rapid guideline published in March 2020 (https://www.nice.org.uk/guidance/ng161) and a desire to reduce the hospital "footfall" during lock down. The longer term consequences of the pandemic are only starting to be realised, such as delay in diagnosis driving higher disease burden states at presentation(76). In particular, the restart of clinical research in the UK has been significantly hampered by compromised research workforce, coupled with delays in research administration. Consequentially, many of the recruiting sites had significant delays in re-opening the trial after the second lock down period. This is clearly demonstrated in Figure 6.2 and 6.5 by the markedly reduced monthly recruitment figures.

Despite the issues highlighted above, the trial completed full recruitment in June of 2022 and the first planned interim analysis is in progress.

Chapter 7

Conclusion

Is a salvage high dose chemotherapy and autologous stem cell transplant (sASCT) an appropriate treatment strategy for patients with relapsed multiple myeloma (MM) after a previous ASCT? The evidence provided in this thesis clearly establishes that a sASCT can not only induce durable second remissions, but improve overall survivorship without a significant impact on quality life. This effect is not equitable across all sub-groups of patients, those with genetic high risk disease deriving no clear benefit over a non-transplant consolidation strategy. Consequential to this published body of evidence, sASCT has been included in both national and international clinical guidelines with increase clinical usage of sASCT in *real-world* data registries. It remains today, 17 years after I designed the evidence-defining trial, an important treatment option for selected patients. In an attempt to derive greater benefit, especially in patient with genetic high risk disease, I designed and fully recruited a follow-on phase III study that will read out in 2023.

Often criticized for the control arm, the use of an almost metronomic dosing of oral cyclophosphamide over 12 weeks did represent a reasonable control to high dose melphalan in an era where fixed duration anti-myeloma chemotherapy was routinely adopted(77, 78). Nonetheless, sASCT is still listed as a treatment option as part of the treatment pathway for MM patients even in 2022(5, 60). However will it persist as a treatment choice in the near future? Will sASCT maintain its role as a standard of care like ASCT in frontline?

The myeloma treatment landscape has grown exponentially over the past decade in particular(9). In particular, the advent of immunotherapy strategies has revolutionized

our thinking of the treatment pathway, as these early phase studies report, we are seeing unprecedented responses in relapsed and refractory, advanced disease(79, 80). Such agents are aimed at T-cell redirection and include chimeric antigen receptor manipulated T-cells and T-cell engager molecules (both Bi-specific T-cell engagers and Bispecific antibodies). The role of such agents in earlier lines of therapy are currently being investigated but the use of such agents is over-shadowed by the immune hostility of the tumour microenvironment and the resulting aberrations in immune function, including immuno-metabolic dysfunctionality(81-84). In this setting of exciting novel therapy developments, I designed a concept for a follow-on clinical trial on completion of UKMRA Myeloma XII ACCoRD trial. This trial aimed to test whether the sASCT still had a role in the face of the new immunotherapy strategies, and the design is illustrated in Figure 7.1. However, due to poor engagement with global pharmaceutical companies who own these new immunotherapy agents, there is no interest in developing this study further. So the question will not be asked in the imminent future.

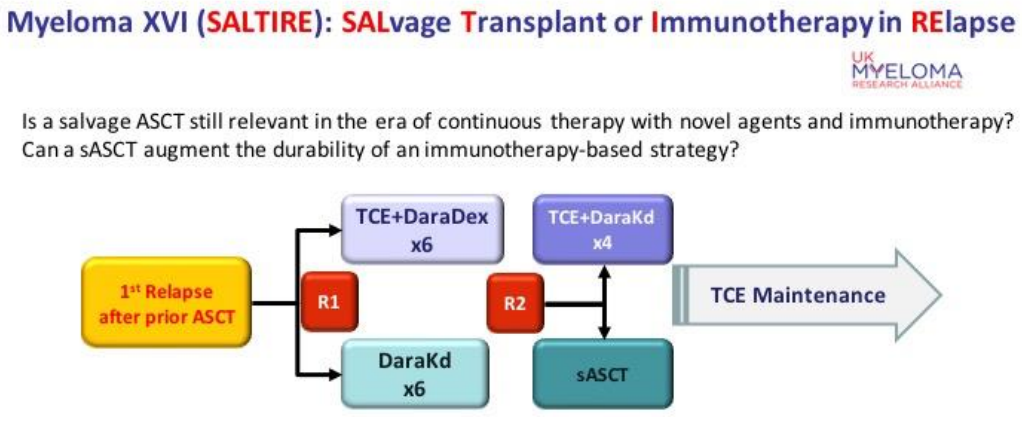

Figure 7.1 Concept design for UKMRA Myeloma XVI SPECTRE trial. TCE: T-cell engager; Dara: daratumumab; Dex/d: dexamethasone; K: carfilzomib

In conclusion, a second or salvage autologous stem cell transplant following high dose melphalan chemotherapy (sASCT) is a viable clinical option to offer patients relapsing after a prior autologous stem cell transplant, though may not offer the best disease management in all patients especially those with genetic high risk disease. The short term impact on quality of life by undergoing such a procedure is time-limited and offset by the demonstrable survivorship benefit. As the treatment landscape evolves at a rapid pace and as we enter the era of immunotherapy, the role of sASCT in the future remains in question.

Chapter 8

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Appendices

Appendix 1: BSBMTCT Salvage autologous stem cell transplant activity (*real-world*)

Appendix 2: Office for National Statistics multiple myeloma survival data

Appendix 3: Key opinion leader testimony (Professor Sergio Giralt)

Appendix 4: Key opinion leader testimony (Professor Mohamad Mohty)

Appendix 5: Key opinion leader testimony (Professor Philip McCarthy)

Appendix 6: RM de Tute*, **G Cook***, JM Brown, J Cavenagh, AJ Ashcroft, JA Snowden, C Williams, K Yong, E Tholouli, M Jenner, A Hockaday, MT Drayson, TCM Morris, AC Rawstron, DA Cairns & RG Owen, on behalf of the National Cancer Research Institute Haemato-oncology Clinical Studies Group. Impact of minimal residual disease (MRD) in relapsed myeloma: results from the NCRI Myeloma X (intensive) trial. (Submitted to *Bone Marrow Transplantation* 2023)