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## Risk and response adapted therapy following autologous stem cell transplant in patients with newly diagnosed multiple myeloma (RADAR (UK-MRA Myeloma XV Trial): study protocol for a Phase II/III randomised controlled trial

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# Risk and response adapted therapy following autologous stem cell transplant in patients with newly diagnosed multiple myeloma (RADAR (UK-MRA Myeloma XV Trial): study protocol for a Phase II/III randomised controlled trial

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## **Abstract**

### **Introduction**

Multiple myeloma is a plasma cell malignancy that accounts for 1-2% of newly diagnosed cancers. At diagnosis, approximately 20% of patients can be identified, using cytogenetics, to have inferior survival (high-risk). Additionally, standard-risk patients, with detectable disease (minimal residual disease (MRD)-positive) post-autologous stem cell transplant (ASCT), fare worse compared to those who do not (MRD-negative). Research is required to determine whether a risk-adapted approach post-ASCT could further improve patient outcomes.

### **Methods**

RADAR is a UK, multi-centre, risk-adapted, response-guided, open-label, randomised controlled trial for transplant-eligible newly diagnosed multiple myeloma patients, using combinations of lenalidomide (R), cyclophosphamide (Cy), bortezomib (Bor), dexamethasone (D) and isatuximab (Isa).

Participants receive RCyBorD(x4) induction therapy, followed by high-dose melphalan and ASCT. Post-ASCT, there are three pathways.

1. A phase III discontinuation design to assess de-escalating therapy in standard-risk MRD-negative patients. Participants receive 12 cycles of Isa maintenance. Those who remain MRD-negative are randomised to either continue or stop treatment.
2. A phase II/III multi-arm multi-stage design to test treatment strategies for treatment escalation in standard-risk MRD-positive patients. Participants are randomised to either; R, RBorD(x4) +R, RIsa, or RBorIsaD(x4) + RIsa.
3. A phase II design to assess the activity of intensive treatment strategies in high-risk patients. Participants are randomised to RBorD(x4) +R or RBorIsaD(x4) + RIsa.

1400 participants will be registered to allow for 500, 450 and 172 participants in each pathway. Randomisations are equal and treatment is given until disease progression or intolerance.

### **Ethics and dissemination**

Ethical approval was granted by the London–Central Research Ethics Committee (20/LO/0238) and capacity and capability confirmed by the appropriate local research and development department for each participating centre prior to opening recruitment. Participant informed consent is required before trial registration and re-confirmed post-ASCT. Results will be disseminated by conference presentations and peer-reviewed publications.

### **Trial registration**

ISCRTN 46841867

**Key Words: Newly Diagnosed, Multiple Myeloma, Transplant-eligible, Risk-adapted, Treatment escalation, Treatment de-escalation**

## **Article Summary**

### **Strengths and limitations of the study**

- Utilises baseline cytogenetic and dynamic MRD-based stratification within its design
  - The genetic risk platform is based on defined adverse lesions detected by FISH (fluorescence in situ hybridization test): t(4;14), t(14;16), t(14;20), del(17p), gain(1q); thus high-risk patients are defined as having at least two of these adverse lesions. For standard risk patients there is stratification after ASCT, based on MRD status.
- Adaptive
  - New experimental treatment arms are expected to be added into the trial as new evidence emerges. At the time of the trial set-up three experimental treatments have been identified in the standard-risk MRD-positive pathway and two experimental treatment strategies have been identified in the genetic high-risk pathway. The current trial size allows for the addition of at least one further experimental treatment strategy in the MRD-positive pathway which incorporates a multi-arm, multi-stage trial design, if all treatment strategies successfully pass to stage 2. There may be the opportunity to add an additional treatment strategy in the high-risk pathways as evidence emerges.
- Trial addresses an unmet need in treatment
  - The majority of patients will respond to an effective induction regimen followed by ASCT, however the key question in RADAR focusses on post ASCT treatment strategies. Patients are stratified to a pathway depending on genetic risk and MRD status and allocated a treatment pathway specific to their response.
- De-escalation strategy –
  - Patients with standard risk disease and MRD negativity after 1 year of maintenance isatuximab will be randomised to stop treatment. Those patients with sustained MRD negativity during a treatment-free period will be assessed with impacts on quality of life and patient well-being.

### **Limitations**

- Poor responders lost in induction phase
  - Patients achieving <PR to induction therapy will not be able to proceed with on-study ASCT and will have to be treated off-trial
- Excludes patients with impaired renal impairment
  - Patients with a CrCl <30 ml/min following correction of reversible causes will be excluded from the trial
- Definition of risk used in the trial may not be aligned to other international definitions, which may limit generalisability of outcomes

## **Introduction**

### **Multiple Myeloma**

Multiple myeloma (MM) is the second most common haematological malignancy with over 5500 patients diagnosed in the UK each year.<sup>1</sup> Whilst there is no established cure, survival has extended markedly in the last 15 years such that patients diagnosed today can expect to live a median of 6 years, and 30% will live for 10 years or longer.<sup>1,2</sup>

These advances have been made possible due to the now standard use of “novel agents” including proteasome inhibitors and immunomodulatory agents (IMiD<sup>®</sup> agents) in conjunction with high-dose melphalan (HDM) supported by autologous stem cell transplantation (ASCT). Whilst MM is predominantly a disease of older people, around 40% of patients are young and fit enough at diagnosis to be eligible for ASCT, a strategy shown in several randomised trials (RCT) to extend progression-free survival (PFS).<sup>2-4</sup>

Improved response rates and increased survival poses challenges for the evaluation of new regimens in a timely manner. Recent studies re-evaluating the role of ASCT in the era of novel agents have confirmed superior PFS in patients allocated to ASCT compared to those allocated to chemotherapy with deferred ASCT.<sup>5</sup> No overall survival (OS) benefit has been seen yet, although this probably reflects the frequent use of salvage ASCT at second remission in most trial patients. Such studies utilise post-ASCT continuous therapy (lenalidomide maintenance)<sup>6</sup> that can extend PFS and OS,<sup>7</sup> but may also impact on quality of life (partly due to treatment-related toxicity), and are not without long-term risk.<sup>8</sup> It is thus imperative to identify those patients who are likely to benefit from extended maintenance therapy, in order to reduce health care costs and minimise toxicity for those who do not benefit.

### **Existing Evidence: Induction Therapy**

Treatment with lenalidomide (R), cyclophosphamide (Cy), bortezomib (Bor) and dexamethasone (D) (RCyBorD) was studied as first line therapy in the Phase 2 EVOLUTION study, where it produced high response rates and deep responses compared to CyBorD or LenBorD.<sup>9</sup>

### **Existing Evidence: High-Risk Patients**

At diagnosis, a small subgroup of patients (approximately 20%) can be identified on the basis of genetic features to have inferior survival regardless of treatment regimen (high-risk patients).<sup>10-12</sup> For such patients, and for those patients with refractory disease (no response to first line therapy), outcomes have remained poor despite the introduction of novel agents<sup>13-15</sup>. Whilst high-risk patients often show a good response to induction therapy, the durability of the response is inferior to standard-risk patients. Using the R-ISS which incorporates high risk cytogenetic features into the the International Staging System (ISS), PFS time is 66 months for R-ISS stage I, 42 months for R-ISS stage II, and 29 months for R-ISS stage III)<sup>16</sup>. The attainment of MRD-negative disease is also critical.<sup>17-19</sup> The activity of the RBorD regimen in patients with high-risk disease looks promising<sup>20</sup>, and there is a question of whether an additional benefit may be gained through the use of anti-CD38 immunotherapy. Anti-CD38<sup>21,22</sup> antibodies have single agent activity, but also impressive efficacy in combination, particularly with IMiD agents, lenalidomide and pomalidomide. In the RADAR trial the anti-CD38 antibody isatuximab (Isa) (SAR650984) will be used. Isatuximab is a naked immunoglobulin (Ig) G1 derived



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3 monoclonal antibody (mAb) that binds selectively to a unique epitope on the human surface antigen  
4 called CD38<sup>23</sup>.  
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### 7 **Existing Evidence: Standard-Risk Patients**

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9 With increasingly effective multi-drug regimens being used for induction treatment, and responses  
10 further deepened following high-dose therapy and ASCT, the major challenge for standard-risk  
11 participants is how to maintain their disease control for as long as possible. The benefit of post-ASCT  
12 consolidation approaches remains controversial, with inconsistent evidence identifying both  
13 appropriate patient groups and treatment strategies.  
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16 Maintenance lenalidomide (R) has been studied within several large studies and has consistently been  
17 shown to increase PFS, confirmed within a recent meta-analysis.<sup>7</sup> The impact of long-term lenalidomide  
18 therapy on bone marrow and immune function, and general wellbeing are not completely understood.  
19 Thus there is an urgent need to identify those patients who benefit most from this approach, as well  
20 as an evaluation of other agents that utilise the host immune system to improve outcomes, such as  
21 antibodies. It is also of benefit to explore the option and effect of stopping maintenance therapy in  
22 patients who have achieved and maintained the deepest response  
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### 26 **Existing Evidence: Use of MRD for stratifying treatment in standard-risk patients**

27 MRD status is a clinically relevant biomarker, and an emerging clinical trial endpoint with recent  
28 guidance published by the International Myeloma Working Group (IMWG).<sup>19 24</sup>  
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31 Several studies have shown that patients who have detectable disease in their bone marrow (MRD-  
32 positive) following ASCT suffer earlier relapses and shorter survival when compared with those who  
33 are MRD-negative.<sup>25 26</sup> These results have been combined in a recent meta-analysis.<sup>26</sup> Hence these  
34 patients should be the focus of investigative strategies aimed at deepening disease response and  
35 converting them from MRD-positive to MRD-negative.  
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39 Patients without detectable disease in their bone marrow (MRD-negative), have longer PFS and OS.<sup>27</sup>  
40 In the IFM2009 study that randomised patients to receive ASCT upfront or to continue chemotherapy,  
41 patients who were MRD-negative fared equally well, regardless of whether they had received ASCT,  
42 or chemotherapy alone. This would suggest that those who have achieved MRD-negative response  
43 may not need to undergo intensive consolidation therapy, and instead may benefit from a de-  
44 escalation of therapy.  
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### 48 **Aims and objectives**

49 RADAR aims to address the most important contemporary therapeutic questions for newly diagnosed  
50 multiple myeloma transplant eligible (NDMM TE) patients post-ASCT by considering three different  
51 post-ASCT treatment pathways:  
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- 54 1. A de-escalation treatment strategy is used to determine whether ceasing Isa maintenance  
55 treatment, after 12 cycles of continuous treatment, is non-inferior to long-term Isa treatment,  
56 in terms of progression-free survival (PFS) in participants who are standard-risk at diagnosis  
57 (participants who have  $\leq 1$  high-risk cytogenetic lesion) and are MRD-negative at 100 days  
58 post-ASCT and 12 months (cycles) after.  
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2. A treatment escalation strategy is used for participants who are standard-risk at diagnosis (participants who have  $\leq 1$  high-risk cytogenetic lesion) and MRD-positive at 100 days post ASCT. The trial aims to compare the activity and efficacy of post-ASCT consolidation and maintenance treatment between combinations of R, Bor, D and Isa to R alone in terms of conversion to MRD-negativity.
3. Dose-intensive consolidation and maintenance strategies will be studied for participants who are high-risk at diagnosis (participants who have  $> 1$  high-risk cytogenetic lesion). The activity of post-ASCT strategies containing R, Bor, D and Isa will be assessed in terms of PFS rate.

## Trial Design

RADAR is a national, multi-centre, risk-adapted, response-guided open-label, randomised controlled trial for NDMM TE patients: phase II/III for standard-risk, MRD-Positive participants, phase III randomised discontinuation design for standard-risk, MRD-Negative participants, phase II randomised for high-risk participants. The following report details the trial protocol and follows the structure of the SPIRIT statement.<sup>28</sup> The SPIRIT checklist can be found within the supplementary material.

## Methods:

### Setting

The RADAR trial will be conducted at 70 centres in the United Kingdom (See supplementary material), as identified via a feasibility assessment to determine those most appropriate to participate in the trial.

Potential participants will be identified by the research team at the time they are referred to the haematology outpatient department with suspected multiple myeloma. A smaller number of participants may be identified during inpatient admissions. Invitation to participate in the trial and provision of information will be made either during their first consultation, when routine diagnostic tests will be performed and potential treatment options discussed, or at the time they receive their diagnostic test results.

### Eligibility criteria

Adults (18 years and older) with previously untreated multiple myeloma requiring therapy, as defined by IMWG diagnostic criteria, who are eligible for stem cell transplant and capable of giving informed consent will be assessed for eligibility. Eligibility will be confirmed prior to; registration, the start of isatuximab maintenance treatment in the Randomisation 1 pathway and each randomisation by the principal investigator (PI) or an appropriately authorised medically trained delegate and will be recorded in the participants' medical records and on the relevant electronic case report form (eCRF).

To be eligible for each point in the trial the participants must meet all the inclusion criteria and none of the exclusion criteria presented in Table 1 for trial registration, Table 2 for isatuximab treatment in the R1 pathway, Table 3 for Randomisation 1 (R1), Table 4 for Randomisation 2 (R2), Table 5 for Randomisation 3 (R3).

Table 1: Inclusion and Exclusion Criteria for Main Trial Registration

<b>Inclusion Criteria:</b>	
1.	Previously untreated patients with multiple myeloma requiring therapy, defined as having myeloma defining events or with biomarkers of malignancy according to IMWG diagnostic criteria
2.	Eligible for stem cell transplant
3.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression);
4.	Total bilirubin $\leq 1.5$ x upper limit of normal (ULN)
5.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3$ x ULN (if ALT <b>and</b> AST are tested, both must meet this criteria)
6.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/L</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/L</math> is allowed),</li> <li>• haemoglobin (Hb) <math>\geq 80g/L</math>. Blood transfusions within 3 days prior to eligibility assessments are <b>not permitted</b>,</li> <li>• platelets <math>\geq 75 \times 10^9/L</math> (in the case of heavy bone marrow infiltration (&gt;50%) which is, in the opinion of the investigator, the cause of the thrombocytopenia and provided appropriate supportive measures and patient monitoring are in place, a platelet count of <math>\geq 50 \times 10^9/L</math> is permitted. Platelet transfusions within 3 days prior to eligibility assessments are <b>not permitted</b>.</li> </ul>
7.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
8.	Able to swallow oral medication
9.	Aged at least 18 years
10.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ol style="list-style-type: none"> <li>a) Are not of childbearing potential (Appendix 7), OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest, OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ol style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Contraception for female and male participants must be in accordance with (and participants must consent to) the Celgene Pregnancy Prevention Plan.</p> <p>If female and of childbearing potential, they must have a negative pregnancy test performed by a healthcare professional within 14 days prior to registration.</p>
11.	Able to provide written informed consent.
<b>Exclusion Criteria</b>	
1.	Asymptomatic (smouldering) MM, monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma of bone, or extramedullary plasmacytoma (without evidence of MM)

2. Received previous treatment for MM, with the exception of local radiotherapy to relieve bone pain or spinal cord compression, prior bisphosphonate treatment, or corticosteroids as long as the total dose does not exceed the equivalent of 160mg dexamethasone. *This criteria is not applicable at R1, R2 and R3 when participants will have received previous treatment for MM as part of this trial.*
3. Unstable angina or myocardial infarction within 4 months prior to registration (or at any time since registration for participants starting isatuximab maintenance, R1, R2 and R3), NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
4. Cardiac disorder identified according to local practice (eg left ventricular ejection fraction, LVEF; results from formal measurements acceptable within 28 days prior to registration)
5. Significant neuropathy (Grade  $\geq 3$ , or Grade 2 with pain)
6. Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to registration. Cancer treated with curative intent for >5 years previously and without evidence of recurrence will be allowed.
7. Pregnant, lactating or breastfeeding female participants
8. Known resistance, intolerance or hypersensitivity to any component of the planned therapies, except in the case of hypersensitivity which is amenable to premedication with steroids or H2 blocker. Intolerance includes hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
9. Major surgery within 14 days before registration (or starting isatuximab maintenance, R1, R2 and R3). This would include surgical intervention for relief of cord compression but does not include vertebroplasty or kyphoplasty.
10. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of trial treatment, including difficulty swallowing.
11. Active systemic infection
12. Participant is hepatitis B surface antigen positive, hepatitis C antibody positive or HIV positive (participants who are hepatitis C core antibody positive but have been successfully treated for the disease may still be eligible – please consult the CTRU/CI). Participants must have hepatitis and HIV screening conducted within 28 days prior to registration.
13. Any other medical or psychiatric condition which, in the opinion of the investigator, contraindicates the participant's participation in this study.
14. Receipt of live vaccination within 30 days prior to registration, for the duration of the study and for 3 months after the last dose of study drug.
15. Participant has risk factors for thromboembolism including the use of agents which may increase their risk of thrombosis, such as hormone replacement therapy (*this exclusion criteria is applicable only at registration and when starting R2 or R3 pathway*)
16. Participant has risk factors for seizures (*this exclusion criteria is applicable only at registration and when starting R2 or R3 pathway*)

Table 2: Inclusion and Exclusion criteria for Isatuximab treatment (R1 Pathway)

<b>Inclusion Criteria:</b>	
<ol style="list-style-type: none"> <li>1. Standard-risk (participant is not <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q), as confirmed by the CTRU.</li> <li>2. 4 cycles of RCyBorD received</li> <li>3. MRD-negative (proportion of malignant cells in the bone marrow is &lt; 1 in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT</li> <li>4. Received <math>\geq 100\text{mg}/\text{m}^2</math> high-dose melphalan and ASCT</li> <li>5. Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG &gt;2 is due to effects of myeloma eg spinal cord compression)</li> <li>6. Total bilirubin <math>\leq 1.5 \times</math> upper limit of normal (ULN )</li> <li>7. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) <math>\leq 3 \times</math> ULN (if ALT <b>and</b> AST are tested, both must meet this criteria)</li> <li>8. Adequate marrow function:               <ol style="list-style-type: none"> <li>a) neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>b) Hb <math>\geq 80\text{g}/\text{L}</math>. Blood transfusions within 3 days prior to eligibility assessments are not permitted,</li> <li>c) platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> </ol> </li> <li>9. Creatinine clearance (CrCl) <math>\geq 30</math> mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)</li> <li>10. Agree to follow the pregnancy prevention guidelines:               <p>Female participants who:</p> <ol style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ol style="list-style-type: none"> <li>e) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest OR</li> <li>f) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest.. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>g) Agree to not donate sperm during the entire study treatment period until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> </li> <li>11. Signed the Informed Consent Document for the R1 treatment pathway.               <ol style="list-style-type: none"> <li>a)</li> </ol> </li> </ol>	
<b>Exclusion Criteria:</b>	
<ol style="list-style-type: none"> <li>1. Disease progression (according to IMWG criteria)</li> <li>2. MRD-positive (proportion of malignant cells in the bone marrow is <math>\geq 1</math> in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT</li> <li>3. Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)</li> </ol>	

Table 3: Inclusion and Exclusion criteria for Randomisation 1

<b>Inclusion Criteria:</b>	
1.	Standard-risk (participant is not <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q), as confirmed by the CTRU.
2.	12 cycles of isatuximab maintenance received
3.	MRD-negative (proportion of malignant cells in the bone marrow is < 1 in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT
4.	MRD-negative (proportion of malignant cells in the bone marrow is < 1 in 100,000, confirmed by HMDS central lab) after 12 cycles of isatuximab
5.	Received $\geq 100\text{mg}/\text{m}^2$ high-dose melphalan and ASCT
6.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression)
7.	Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN)
8.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3 \times$ ULN (if ALT and AST are tested, both must meet this criteria)
9.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>• Hb <math>\geq 80\text{g}/\text{L}</math>. Blood transfusions within 3 days prior to eligibility assessments are not permitted,</li> <li>• platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> </ul>
10.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
11.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ul style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 5 months after the last dose of study drug, OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject from the time of signing the informed consent form until 5 months after the last dose of study drug. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 5 months after the last dose of study drug.</li> </ul> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ul style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 5 months after the last dose of study drug, OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 5 months after the last dose of study drug. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until 5 months after the last dose of study drug.</li> </ul>
12.	Signed the Informed Consent Document for the R1 treatment pathway.
<b>Exclusion Criteria</b>	
1.	Disease progression (according to IMWG criteria)
2.	MRD-positive (proportion of malignant cells in the bone marrow is $\geq 1$ in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT or after 12 cycles of isatuximab
3.	Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)

Table 4: Inclusion and Exclusion Criteria for Randomisation 2

<b>Inclusion Criteria:</b>	
1.	Standard-risk (participant is not <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q) as confirmed by CTRU.
2.	4 cycles of RCyBorD received
3.	MRD-positive (proportion of malignant cells in the bone marrow is $\geq 1$ in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT
4.	Received $\geq 100\text{mg/m}^2$ high-dose melphalan and ASCT
5.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression)
6.	Total bilirubin $\leq 1.5$ x upper limit of normal (ULN )
7.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3$ x ULN (if ALT and AST are tested, both must meet this criteria)
8.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>• Hb <math>\geq 80\text{g/L}</math></li> <li>• platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> </ul>
9.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
10.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ul style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ul style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul>
11.	Signed the Informed Consent Document for the R2 treatment pathway.
<b>Exclusion Criteria:</b>	
1.	Disease progression (according to IMWG criteria)
2.	Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)

Table 5: Inclusion and Exclusion criteria for Randomisation 3

<b>Inclusion Criteria:</b>	
1.	High-risk (participant is <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q)) as confirmed by CTRU.
2.	4 cycles of RCyBord received
3.	Received $\geq 100\text{mg/m}^2$ high-dose melphalan and ASCT
4.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression)
5.	Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN )
6.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3 \times$ ULN (if ALT and AST are tested, both must meet this criteria)
7.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>• Hb <math>\geq 80\text{g/L}</math></li> <li>• platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> <li>• Creatinine clearance (CrCl) <math>\geq 30 \text{ mL/minute}</math>, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)</li> </ul>
8.	Creatinine clearance (CrCl) $\geq 30 \text{ mL/minute}$ , according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
9.	Agree to follow the pregnancy prevention guidelines: <p style="margin-left: 20px;">Female participants who:</p> <ul style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul> <p style="margin-left: 20px;">Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ul style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul>
10.	Signed the Informed Consent Document for the R3 treatment pathway.
<b>Exclusion Criteria</b>	
1.	Disease progression (according to IMWG criteria)
2.	Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)



## Interventions and Dosing

### *Intervention Schedule*

All participants will receive four, 21 day, cycles of induction treatment with RCyBorD. During this time, the genetics risk status of the participant will be analysed and determined from bone marrow samples prior induction treatment (from diagnosis or trial-specific procedures). Participants will either be allocated as high risk (defined as the presence of at least 2 of these adverse lesions: t(4,14), t(14,16), t(14,20), del(17p) or gain(1q)) or standard risk. At the end of the induction cycle participants will be assessed for response. In the absence of disease progression or intolerance, participants with at least a partial response (PR) will proceed to HDM and ASCT which will be carried out according to local practice. At 100 days post-ASCT participants will be assessed for MRD and response and will follow one of three pathways of post ASCT treatment, provided they meet the eligibility criteria:

1. Participants identified as standard risk and who are MRD-negative post-ASCT will be treated according to the R1 pathway. All participants will receive 12 cycles of Isa maintenance treatment. Those who remain MRD-negative following cycle 12, will be randomised to continue or stop Isa maintenance treatment.
2. Participants identified as standard-risk and who are MRD-positive post-ASCT and have at least a minimal response (MR) at 100 days post ASCT, will proceed to R2. Eligible participants will be randomised between: R maintenance; RBorD consolidation and R maintenance (RBorD + R); RIsa maintenance; or RBorIsaD consolidation and RIsa maintenance (RBorIsaD + RIsa).
3. Participants identified as high-risk and have at least a partial response (PR) at 100 days post ASCT will proceed to R3. These participants will be randomised to receive either RBorD consolidation, followed by R maintenance; or RBorIsaD consolidation followed by RIsa maintenance.

All randomisations are balanced across the treatment arms. A computer generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well balanced for the stratification factors of each randomisation (See Table 6).

Table 6: Stratification Factors

Randomisation:	Stratification factors:
1	<ul style="list-style-type: none"> <li>• Centre</li> <li>• Number of high risk lesions at trial registration (0 or 1 or unable to determine)</li> </ul>
2	<ul style="list-style-type: none"> <li>• Centre</li> <li>• Number of high risk lesions at trial registration (0 or 1 or unable to determine)</li> <li>• Response at 100 days post-ASCT (<math>&lt; VGPR</math>, <math>\geq VGPR</math>)</li> </ul>
3	<ul style="list-style-type: none"> <li>• Centre</li> <li>• Number of high risk lesions at trial registration (2, or <math>\geq 3</math>, or unable to determine)</li> <li>• Response at 100 days post-ASCT (<math>&lt; VGPR</math>, <math>\geq VGPR</math>)</li> </ul>

Table 7 summarises the starting doses for the induction treatment and each post-ASCT treatment pathway. Following ASCT all treatments will continue until disease progression or intolerance. Response will be assessed at the end of each cycle according to the IMWG 2016 response criteria<sup>24</sup><sup>29-31</sup>. Treatment intolerance will be assessed throughout each treatment cycle, according to the national cancer institute (NCI) common terminology criteria for AE (CTCAE) Version 5. All consolidation cycles are 21 days in length, maintenance cycles are 28 days in length.

Table 7: Dosing schedule for R<sub>Cy</sub>BorD induction and each randomisation pathways

<b>Trial Registration- Induction (Each cycle = 21 days)</b>		
<b>Treatment (Route)</b>	<b>Induction – All participants (Starting Dose)</b>	<b>Days</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup>	1, 8, 15
<b>Cyclophosphamide (PO)</b>	500mg	1, 8
<b>Lenalidomide (PO)</b>	25mg	1-14
<b>Dexamethasone (PO)</b>	40mg	1, 8, 15
<b>Isatuximab Pre-Randomisation 1 (Each cycle = 28 day)</b>		
<b>Treatment (Route)</b>	<b>R1 pathway participants Only (Starting Dose)</b>	<b>Days</b>
<b>Isatuximab (IV)</b>	10mg/kg	1, 8, 15 and 22 cycle 1 then days 1 and 15 from cycle 2 onwards
<b>Randomisation 1: Isatuximab maintenance (Each Cycle = 28 days)</b>		
<b>Treatment</b>	<b>Isatuximab (Days)</b>	<b>“Stop Isatuximab” (Days)</b>
<b>Isatuximab (IV)</b>	10mg/kg (Day 1 Only)	None
<b>Randomisation 2: MRD-positive treatment escalation pathway</b>		
<b>Treatment Arm 1 (Control) : Lenalidomide (R) maintenance</b>		
<b>Treatment (Route)</b>	<b>Starting Dose (Days)</b>	
<b>Lenalidomide (PO)</b>	10mg/kg* (1-21 )	
<b>Treatment Arm 2: R<sub>BorD</sub> consolidation + R Maintenance</b>		
<b>Treatment</b>	<b>Consolidation: Cycle 1-4 (each cycle = 21 days)</b>	<b>Maintenance (each Cycle = 28 days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)
<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA
<b>Treatment Arm 3:R<sub>ISa</sub> Maintenance</b>		
<b>Treatment</b>	<b>Maintenance (Days)</b>	
<b>Lenalidomide (PO)</b>	10mg* (Day 1-21)	
<b>Isatuximab (IV)</b>	10mg/kg (1, 8, 15 and 22 cycle 1 then days 1 and 15 from cycle 2 onwards)	
<b>Treatment Arm 4: R<sub>BorD</sub> + R<sub>ISa</sub></b>		
<b>Treatment</b>	<b>Consolidation Cycle 1-4: Each cycle = 21 days (Days)</b>	<b>Maintenance: Each cycle = 28 days (Days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)
<b>Isatuximab (IV)</b>	10mg/kg (1, 8, 15 cycle 1 then days 1 and 8 cycle 2, then days 1 and 15 cycle 3 onwards)	10mg/kg (1 and 15)
<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA
<b>Randomisation 3: High Risk Treatment Pathway</b>		
<b>Treatment Arm 1: R<sub>BorD</sub> Consolidation and R maintenance</b>		
<b>Treatment</b>	<b>Consolidation: Cycle 1-4 (each cycle = 21 days)</b>	<b>Maintenance (each Cycle = 28 days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)

<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA
<b>Treatment Arm 2: RBorIsaD consolidation + RIsa Maintenance</b>		
<b>Treatment</b>	<b>Consolidation Cycle 1-4: Each cycle = 21 days (Days)</b>	<b>Maintenance: Each cycle = 28 days (Days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)
<b>Isatuximab (IV)</b>	10mg/kg (1, 8, 15 cycle 1 then days 1 and 8 cycle 2, then days 1 and 15 cycle 3 onwards)	10mg/kg (1 and 15)
<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA

\*or final dose administrated at the end of induction or consolidation treatment if lower

### *Intervention Adherence*

Throughout the trial R will be taken orally and swallowed whole at the same time on the scheduled days. D and Cy will be taken orally, whilst Bor will be administrated via a subcutaneous injection. Bortezomib may also be administered at home if this is in line with local policies and if appropriate procedures are in place. Isa will be given as an intravenous infusion and at a facility capable of managing hypersensitivity reactions.

To monitor adherence to the oral trial medicines, participants will complete a participant diary card which will be reviewed at each trial visit. Non-compliance will be reported to the CTRU and any unused capsules will be returned to the pharmacy.

### *Dose Modifications and Discontinuations*

With the exception of Isa, which can only be interrupted and resumed, dose modifications are permitted in the management of toxicities. When the dose of any drug is reduced the dose cannot be re-escalated in this trial.

If one drug in a combination is stopped, treatment with the other drugs in combination can continue. Scenarios in which the participant may remain on trial following consultation with the Chief Investigator (CI) are if they: discontinue two or more drugs during combination therapy; cease treatment for more than three weeks in between any treatment cycle or are delayed in starting maintenance of consolidation beyond 120 days post-ASCT. Note that if Bor, R or D is stopped during the pre-ASCT induction treatment due to toxicity, the participant will only be able to be treated on the standard-risk-MRD-negative pathway (assuming they meet the relevant inclusion criteria).

If treatment is discontinued early, the participant will be treated off trial at the discretion of their treating clinician.

### *Concomitant medication:*

Local support care protocols, including anti-emetic schedules, tumour lysis syndrome prevention, venous thromboembolism prophylaxis and prophylactic antimicrobial therapy should be followed. The excluded concomitant medications and procedures whilst receiving trial treatment are listed in supplementary material.

Concomitant medication, disease and other malignancies will be recorded at eligibility.

## Outcomes:

### *Primary outcomes*

PFS-R1 is defined as the time from R1 to the time of first documented evidence of disease progression or death from any cause. Individuals who are lost to follow-up or progression-free at the time of analysis will be censored at their last known date to be alive and progression-free.

Attainment of MRD-negativity is defined as a binary endpoint. MRD-negativity will be determined at 6 months post-R2 (end of cycle 6 post-ASCT treatment for participants allocated to maintenance only strategies and end of cycle 7 post-ASCT treatment for participants allocated to maintenance and consolidation strategies) according to the IMWG 2016 response criteria.

The PFS rate is defined as the proportion of participants who are alive and progression-free 28 months post-R3.

Disease progression is defined according to the IMWG 2016 response criteria for Multiple Myeloma<sup>24 29-31</sup>.

### *Secondary outcomes:*

The secondary outcomes of this trial are to assess; PFS for R2 and R3, Time to progression, Time to second PFS event (PFS2), Overall survival (OS), Survival after progression, Objective response rate (ORR), Attainment of Very Good Partial Response ( $\geq$  VGPR), Attainment of MRD negativity, Time to improved response, Time to next treatment, Treatment compliance and total amount of therapy delivered, Toxicity and Safety, including the incidence of second malignancies, Quality of life (QoL) including EORTC-QLQ-C30, EORTC-QLQ-MY20 and EQ-5D-3L and Cost effectiveness.

### *Exploratory and subgroup analyses*

An overview of the planned exploratory and subgroup analysis can be found in the supplementary material. These include genetic and molecular analysis of participant samples conducted by the respective central laboratories, as well as additional analysis to review the infection and re-infection rates of covid-19 in participants during induction, post-ASCT and during post ASCT consolidation.

## Participant's timelines

The full trial schema can be seen in Figure 1. The schedule of assessments at each time point are presented in Figure 2.

### *Trial Entry*

Participants will enter into the trial at one of two points in their pathway, this will either be at bone marrow registration or at main trial registration.

### *Trial Consent*

Participants who enter the trial at bone marrow registration will provide consent to have bone marrow samples taken and sent to central laboratories for analysis. If the participant does not have myeloma

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2  
3 or decides to not take part in RADAR, they will have the option of consenting to their samples being  
4 used in future research.  
5

6  
7 All participants will be required to provide written informed consent for the trial prior to trial  
8 registration (for initial trial treatment and further trial information) and prior to starting their post-  
9 ASCT treatment pathway once their post-ASCT assessments have been completed (for their pathway  
10 specific treatment). Optional consent regarding QoL and healthcare resource use questionnaires and  
11 the use of samples for future research will also be obtained within the first consent process.  
12  
13

14  
15 Consent forms are included in supplementary material.  
16

### 17 *Trial Registration*

18 Following initial consent, participant eligibility for trial registration will be assessed. Trial samples for  
19 blood and urine will be taken for all participants and bone marrow samples will be taken for those  
20 who did not enter the trial through bone marrow registration.  
21  
22

### 23 **Genetic Risk**

24 Bone marrow samples from diagnosis will be analysed at time of diagnosis at local cytogenetics  
25 laboratories for FISH-defined high-risk makers. Original/copy of the FISH testing report will also be  
26 sent to CTRU where they will be reviewed by the CI/Trial management team for risk stratification.  
27 Participants will either be categorised high-risk (defined as the presence of at least 2 of the following  
28 adverse lesions: t(4;14), t(4;16), t(14;20), del(17p) or gain(1q)) or standard-risk.  
29  
30  
31

32  
33 Participants will commence RCyBorD treatment once a diagnosis of symptomatic myeloma has been  
34 confirmed by the treating physician, and ideally when it is known that the FISH testing has been  
35 successful.  
36  
37

38 Where risk status can be determined from the first sample participants can continue on the trial. If  
39 status cannot be confirmed and the FISH report shows a full test failure i.e. no information relating to  
40 adverse lesions is available, a second attempt will be made to collect a bone marrow sample prior to  
41 treatment starting. If partial results are obtained from the FISH sample, it may be possible that the CI/  
42 trial management group (TMG) will be able to determine risk status using the assumption that  
43 translocations are mutually exclusive and that some markers are rare. If risk status can be determined  
44 a second bone marrow sample is not required. However, this must be confirmed by the CTRU.  
45  
46  
47

48 If, after two bone marrow samples, the FISH results for some or all the adverse lesions are inconclusive  
49 participants risk will be determined using a combination of the results from the two samples. The most  
50 appropriate pathway will be determined by the CI. Note this may result in the participants  
51 stratification factor being 'unable to determine' at randomisation. If a second bone marrow has been  
52 requested by CTRU but the collection was not attempted, the participants will be taken off the study  
53 (after ASCT, if induction treatment was already started)  
54  
55  
56

### 57 *Induction and ASCT*

58 Following trial registration, once all central samples have been taken and risk status confirmed,  
59 participants will receive induction treatment as described in the intervention section. In the absence  
60

1  
2  
3 of disease progression or treatment intolerance participants with at least a partial response (PR) to  
4 will proceed to HDM and ASCT.  
5

6  
7 Consenting participants will complete QoL and resource use questionnaires at the end of RCyBorD  
8 induction treatment.  
9

10  
11 All participants who go through ASCT will have a bone marrow sample taken at 100 days (+/- 14) post-  
12 ASCT. If an MRD result cannot be obtained at the first attempt, the bone marrow will be repeated  
13 once (within 28 days after 100 days post-ASCT time point). If the second attempt fails, the participant  
14 will be considered MRD-positive.  
15

#### 16 17 *Post-ASCT Treatment*

18  
19 Participants who receive all 4 cycles of induction treatment followed by ASCT will be assessed for  
20 eligibility into their assigned randomisation pathways determined by genetic risk and MRD results and  
21 treated as described in the intervention schedule.  
22

23  
24 Consenting participants in the R1 pathway will complete QoL and resource use questionnaires after  
25 cycle 6, 12, 24 and 36 (participants randomised to “stop Isa” will complete the cycle 24 and 36 QoL  
26 and resource use questionnaires at equivalent time points).  
27

28  
29 Similarly, consenting participants to receive R or RIsa within pathway R2 and R3 will complete QoL and  
30 resource use questionnaires after cycles 6, 12 and 24 of maintenance. Those randomised to receive  
31 RBorIsa+R or RBorIsaD+RIsa will complete QoL and resource use questionnaires after cycles 3, 9 and  
32 21 of maintenance.  
33

#### 34 35 *Trial Follow-up*

36  
37 Participants who discontinue during induction and until 100 days post-ASCT will be followed up for  
38 data pertaining to safety, details of salvage treatment, progression (including second progression),  
39 and survival at standard care visits. Follow ups will be conducted every 2 months up until disease  
40 progression, death or the end of trial. Similar follow-up will be completed for participants who  
41 discontinue their allocated trial treatment, which started post-ASCT. In addition consenting  
42 participants will still complete QoL and resource use questionnaires at appropriate time points.  
43

44  
45 All types of adverse event/reaction will be collected until 60 days after the last dose of protocol  
46 treatment.  
47

48  
49 Following disease progression all participants will be followed up annually until death, or until the end  
50 of the trial.  
51

#### 52 53 **Sample size**

54  
55 In total 1400 participants will be recruited into the trial. Accounting for participants who will be lost  
56 to follow-up, this allows for 500, 450 and 172 participants to enter each randomisation, respectively.  
57  
58  
59  
60

### Randomisation 1

Data from our previous trial Myeloma XI, suggests that approximately 50 participants will lose their MRD-negative status during the first 12 cycles of Isa maintenance. In addition, Myeloma XI estimated median PFS with continuous R to be 50 months amongst TE participants.<sup>32</sup> Under these assumptions and allowing for our randomisation being 12 months later, 500 participants allows for 80% power to test a non-inferiority margin of 10% at 2 years post-R1 (this equates to a hazard ratio of 1.38) with a one-sided 5% significance level, allowing for approximately 20% further drop-out after R1 amongst participants unwilling to cease treatment or being lost to follow-up.

A power of 80% will be attained when 238 PFS events have been observed. These calculations assume that PFS follow an exponential distribution and that there will be 3 years of recruitment to R1 and 2 further years of follow-up (in order that all participants can have PFS at 2 years post-R1 assessed).

Global Health Status/Quality of Life is considered a key secondary endpoint of R1 as the conclusion that the cessation of continuous treatment is non-inferior should not come at the expense of quality of life. Ignoring those required to account for participants lost to follow-up, the 406 participants recruited above give >95% power to detect a difference of 10 points at 2 years post-R1, where 10 points represents an accepted medium magnitude clinically relevant difference.<sup>33</sup> The calculation uses data collected from the intensive pathway of MRC Myeloma IX to estimate that the standard deviation in the Global Health Status/QoL subscale of EORTC-QLQ-C30 as 27.54 along with a two-sided 5% significance level.<sup>34</sup>

### Randomisation 2

R2 is a multi-arm, multi-stage drug/drug-combination assessment platform with seamless phase II (activity) and phase III (efficacy) stages. Each experimental arm is compared with a designated control arm (R maintenance).

Early data from Myeloma XI and similar data from IFM/DFCI 2009<sup>35</sup> suggest that a 10% upgrade in MRD-negative rate after 6 months continuous R treatment is achievable. It is thought that RBoRD consolidation followed by attenuated continuous R or continuous R combined with antibody or immunotherapy could lead to a 30% increase in MRD-negative rate, a 20% upgrade of increase at 6 months post-randomisation when compared to continuous R treatment, as good as therapy combinations containing an alternative proteasome inhibitor.<sup>33</sup>

Following the strategy of Bratton and colleagues<sup>36</sup> for a multi-arm multi-stage trial with:

- N=2 stages (Stage 1 (activity) and Stage 2 (efficacy)) and
- J=4 experimental arms (RBoRD+R, R+Isa, RBoRIsaD + RIsa and TBC) and a single control arm (R)
- Where allocation is equal across each arms (1:1:1:1:1) and
- The power in Stage 1 and Stage 2 is 95% and 85%, respectively,
- the one-sided significance level in Stage 1 and Stage 2 is 25% and 1%, respectively,
- 10 participants per month are entered at R2, Stage 1 (activity) analysis and reporting requires 1 month and 5% of participants drop-out.

1  
2  
3 This equates to 40 participants in each arm at Stage 1 and 50 further participants in each arm at Stage  
4 2. This will require a maximum of 46 months of recruitment plus a further 6 months of follow-up for  
5 the final participant. Overall, this design has a power of 83.4% and a one-sided family-wise error rate  
6 (FWER) of ~3%.  
7  
8

9  
10 Randomisation 2 has been powered assuming four experimental arms and that all experimental arms  
11 will continue to stage 2. In the case that only three experimental arms are implemented or at least  
12 one experimental arm is concluded to show a lack of activity after stage 1, the trial will have a higher  
13 power than stated above.  
14  
15

### 16 *Randomisation 3*

17 Each arm of R3 will take the form of one-stage treatment design proposed by Simon, Wittes and  
18 Ellenberg<sup>37</sup> where the A'Hern design<sup>38</sup> is first implemented to determine treatment activity in both  
19 arms. Treatment activity will be determined by considering the PFS rate at 28 months. Data from  
20 Myeloma XI demonstrated a median PFS for high-risk participants in the intensive pathway of  
21 approximately 19 months (unpublished data). It is thought that for the treatments proposed to be  
22 investigated further in a Phase III trial they should increase the median PFS from 19 months to at least  
23 28 months (9 month increase), i.e. increasing the PFS rate at 28 months from 34.7% to 50%.  
24  
25  
26  
27

28 In order to have an 80% power of demonstrating that the one-sided 95% confidence interval of the  
29 PFS rate at 28 months excludes 34.7%, 81 evaluable participants are required, where a treatment arm  
30 will be deemed a "success" if at least 37 out of 81 participants are progression-free at 28 months. To  
31 account for approximately 5% of participants being unevaluable at 28 months post-R3, 86 participants  
32 will be randomised to each treatment arm i.e. 172 participants are required to be entered into R3.  
33  
34

### 35 *Total Study Sample Size*

36 Accounting for those participants who will be lost-to-follow-up R1, R2 and R3 require 500, 450, and  
37 172 participants to enter each randomisation respectively.  
38  
39

40 Considering R1 and R2, it is assumed that 50 participants will lose their MRD-negative status during  
41 the 12 months of continuous treatment (Myeloma XI, unpublished data). Therefore 550 participants  
42 are required to enter the MRD-negative part of the standard-risk pathway. It is assumed that 55% of  
43 standard-risk participants will be MRD-negative at the point of assessment therefore approximately  
44 1000 participants are required to reach the MRD assessment stage of the standard-risk pathway<sup>35 39</sup>  
45 It is assumed that 90% of all those recruited will reach this point therefore 1112 participants are  
46 required to enter the standard-risk pathway<sup>5</sup>. It is anticipated that 80% of all those recruited will be  
47 standard-risk (Myeloma XI, unpublished data) therefore at least 1390 participants are required to be  
48 recruited to the trial. Rounding this we obtain an overall sample size of 1400.  
49  
50  
51

52 This gives 280 participants who are expected to enter the high-risk pathway, using the same logic as  
53 in the standard-risk pathway if 90% of participants reach R3 then there will be approximately 252  
54 participants recruited to R3. Given the calculations above it is plausible that another arm could be  
55 added to the high-risk pathway at a later date.  
56  
57  
58

### 59 *Recruitment:*



1  
2  
3 It is planned that 1400 participants will be recruited for a total of 36 months. Once all centres are  
4 open, the recruitment target is 38 participants a month (equating to approximately 30 standard risk  
5 and 8 high-risk participants).  
6  
7

8 In order to ensure the trial will meet the target sample size within the recruitment period, site set-up  
9 was prioritised whilst the trial was preparing to open to recruitment. In addition, the trial team are  
10 actively engaging with Principal Investigators at sites who support the trial to ensure that those sites  
11 open quickly and are maintaining regular communication with open sites to ensure that they continue  
12 to recruit to the trial.  
13  
14

15  
16 The trial opened to recruitment on 11/05/2021.  
17

### 18 **Assignment of treatment allocations:**

19  
20 Each of the registration and randomisation procedures will be conducted centrally using the University  
21 of Leeds Clinical Trial Research Unit (CTRU) automated 24-hour web base and telephone system.  
22  
23

### 24 **Registration**

25 If a patient is suspected to have myeloma they will enter the trial at the time of routine diagnostic  
26 tests, through bone marrow registration. Once diagnosis is confirmed locally and the research team  
27 consider the patient potentially eligible for the trial, patients will be provided with full verbal  
28 explanation of the trial and full participant information sheet and informed consent documents to  
29 consider. Once the patient has provided informed consent to the first stage of the trial they will be  
30 registered into the trial at Bone Marrow Registration.  
31  
32  
33

34 Patients who have already had Myeloma confirmed prior to being approached for the trial, and those  
35 who decline consent at bone marrow registration, will enter at main trial registration.  
36  
37  
38

### 39 **Data Collection**

40 Data collection will primarily be via Remote Data Entry (RDE) on electronic case report forms (eCRFs),  
41 provided by the CTRU at the University of Leeds, and will be entered by staff at the research site.  
42 Access to the live RADAR database will be provided by the CTRU following sites being authorised to  
43 open to recruitment; guidance on RDE and completing eCRFs will be provided. Data regarding  
44 informed consent, QoL, Healthcare Resource Use questionnaires and in-patient stay forms will be  
45 collected via paper case report forms.  
46  
47  
48

49 QoL and Healthcare Resource Use questionnaires will be completed by the participant in clinic or at  
50 home and sealed in an envelope before handing back to the site research team who will return them  
51 to the CTRU via post.  
52  
53

### 54 **Data Management**

55 All information collected during the course of the trial will be kept strictly confidential. Information  
56 will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of  
57 the Data Protection Act 2018.  
58  
59  
60

1  
2  
3 Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it  
4 is received, confirmed as not available or the trial is at analysis. The CTRU/Sponsor will reserve the  
5 right to intermittently conduct source data verification exercises on a sample of participants, which  
6 will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access  
7 to participant notes at the participating hospital sites and the ongoing central collection of copies of  
8 Informed Consent Documents and other relevant investigation reports.  
9  
10

## 11 12 **Statistical methods**

13  
14 Statistical analysis is the responsibility of the CTRU statisticians, with the exception of the cost-  
15 effectiveness analysis, which will be undertaken by the health economists at the University of Leeds.  
16 A full statistical analysis plan (SAP) and Health Economics Analysis Plan (HEAP) will be written and  
17 approved before any analyses are undertaken.  
18  
19

20 The analysis population will depend on the randomisation. Separate intention to treat (ITT), per  
21 protocol (PP) and safety populations will be defined for each randomisation. In either case the ITT  
22 population will include participants according to their randomisation allocation, regardless of  
23 eligibility whether they prematurely discontinued the treatment, or did not comply with the regimen.  
24 The PP population will exclude individuals who do not receive their randomisation allocation or who  
25 are found to be ineligible following randomisation. The safety population will consist of all participants  
26 who receive at least one dose of the trial treatments and analyse participants according to what they  
27 received rather than what they were randomised to.  
28  
29  
30

31  
32 With the exception of two interim analyses, no other formal analysis is planned until participants have  
33 attained the primary endpoint for each of the randomisations.  
34  
35

### 36 *Primary endpoint analyses*

#### 37 Randomisation 1

38  
39 The primary endpoint for R1 will be attained 2 years after the final participant has been randomised  
40 to R1.  
41  
42

43 As R1 is a non-inferiority trial, both PP and ITT population analyses will be used as co-primary analyses  
44 and both are required to demonstrate statistical significance of non-inferiority where any  
45 discrepancies will be reported.  
46  
47

48 PFS at R1 will be assessed using Cox proportional hazards regression to adjust for the stratification  
49 factors of R1 excluding centre, and presented using Kaplan-Meier estimates of the survival function.  
50 The treatment cessation strategy will be declared non-inferior to the continuous treatment strategy  
51 if the upper bound of the one-sided 95% confidence interval for the hazard ratio is less than 1.38. Note  
52 no adjustment will be made for interim analysis due to it being a test for inferiority (see below) and  
53 not non-inferiority.  
54  
55  
56

#### 57 Randomisation 2

58 The primary endpoint for R2 will be attained 6 months after the final participant has been randomised  
59 to R2. Primary analysis will be undertaken on the ITT population.  
60

1  
2  
3  
4 An overall one-sided approximately 3% FWER will be applied accounting for each pair-wise  
5 comparison over each stage and all comparisons. This equates to a 25% and 1% one sided significance  
6 level at interim and final analysis. MRD-negative rate will be compared between each pair-wise  
7 comparison (experimental vs control) in turn using logistic regression and adjusted for the  
8 minimisation factors of R2 excluding centre.  
9  
10

### 11 12 Randomisation 3

13  
14 The primary endpoint for R3 will be attained 28 months after the final participant has been  
15 randomised to R3.  
16

17  
18 Primary analysis will be undertaken on the ITT population. The number of participants who are alive  
19 and progression-free at 28 months post R3 will be summarised separately within each treatment arm  
20 and exact one sided 95% confidence intervals calculated. The null hypothesis is that the percentage  
21 of participants alive and progression-free at 28 months post R3 is 34.7%. A treatment arm is deemed  
22 a “success” if the one sided 95% confidence intervals of the PFS rate at 28 months excludes 34.71%.  
23 The treatment will then be proposed to be investigated further in a phase III trial.  
24  
25

26  
27 No multiple imputation is planned for the primary endpoints.  
28

### 29 *Secondary endpoint analyses*

30 Overall survival and other time-to-event endpoints will be analysed using methods similar to those  
31 described for progression-free survival. All binary endpoints will be analysed using similar methods to  
32 those described for the attainment of MRD negativity endpoint.  
33  
34

35  
36 For both R1 and R3, each experimental arm will be independently compared to historical control data  
37 using molecularly matched individual participant data (IPD) from Myeloma XI+(TE) and assessed for  
38 superiority in terms of progression-free survival. Further details of the molecular matching of IPD will  
39 be described in the statistical analysis plan, but it is anticipated that propensity score matching may  
40 be an appropriate technique. In each case a one-sided 10% significance level will be applied for each  
41 comparison with historical data.  
42  
43

44  
45 The number and proportion of participants in each response category will be summarised by allocated  
46 treatment and exact 95% two-sided confidence intervals will be calculated. The difference in  
47 proportions for each response category will be presented with corresponding 95% two-sided  
48 confidence intervals.  
49

50  
51 Quality of life will be summarised using mean scores adjusted for baseline and two-sided 95% CI for  
52 each EORTC QLQ-C30 and EORTC QLQ-MY20 module symptom, role and functioning domain at each  
53 assessment time-point. Similar summaries will be produced for quality-adjusted life years (QALYs) as  
54 scored by the EQ-5D 3 Level (EQ-5D-3L) questionnaire. For the key secondary analysis of R1, the Global  
55 Health Status / Quality of Life subscale at two years post-R1, will be compared between the arms using  
56 a multivariable linear regression model, adjusting for the R1 stratification factors.  
57  
58  
59  
60

### *Exploratory and subgroup analyses*

A series of subgroup and exploratory analyses will be undertaken. Subgroup analyses will follow the same structure as the main analysis of the respective endpoint. Where appropriate interaction terms will be added to the regression models to account for the subgroup being investigated. Subgroup and exploratory analyses may, by chance, generate false negative or positive results. Those carried out will be interpreted with caution.

The analysis for the exploratory outcomes will be detailed in the SAP.

### **Health economics**

The economic evaluation will take a decision modelling approach to assess the cost-effectiveness of treatment options for risk stratified treatment vs standard non-stratified treatment over participants' lifetime. This will allow several research questions to be incorporated within one model. The model will be developed using best practice<sup>40</sup> and the model structure, health states and parameter values will be derived from the trial outputs, published literature, and expert clinical opinion. Data to model stratified treatment options will be drawn from the RADAR trial results while parameters for standard non-stratified treatment will be obtained from the wider literature.

Reflecting the main trial analysis of effectiveness, the economic evaluation will assess the cost-effectiveness of treatment options at each of the randomisations in RADAR. For standard risk participants at R1, the cost-effectiveness analysis will compare treatment with isatuximab for 12 cycles only to long-term isatuximab treatment, continued until disease progression. For standard risk participants who are MRD-positive at 100 days post-ASCT in terms of conversion to MRD negativity at R2, the cost-effectiveness of post-ASCT consolidation and maintenance treatments in the treatment of standard-risk participants will be evaluated. For high-risk participants at R3, the cost-effectiveness of post-ASCT consolidation and maintenance treatment strategies containing lenalidomide, bortezomib, dexamethasone and isatuximab separately will be evaluated. In addition, the cost-effectiveness of stratified treatment pathways will be compared with standard non-stratified treatments.

All analyses will be conducted following NICE reference case guidelines<sup>41</sup>. As such, outcomes will be measured in QALYs based on EQ-5D<sup>42</sup> and EORTC QLQ-C30<sup>43</sup> utilities and costs will be calculated from a health and personal social services perspective. Cost-effectiveness will be determined in comparison to the NICE cost-effectiveness threshold of £20,000 per QALY gained. Deterministic and probabilistic (using Monte Carlo simulations) sensitivity analyses will be conducted to explore the impact of parameter value changes on estimates of cost-effectiveness and to determine the level of uncertainty around the results of the lifetime analysis. In addition, value of information analysis will be conducted to estimate the value of further research.

### **Trial Oversight**

The TMG includes the CI, CTRU team and co-investigators that are assigned responsibility for the clinical set up, ongoing management, promotion of the trial and interpretation of the results. The trial steering committee (TSC), consisting of independent clinicians and statisticians, will provide overall

1  
2  
3 supervision on the trial, including trial progress, adherence to protocol, participant safety and  
4 consideration of new information.  
5  
6

### 7 **Data Monitoring**

8  
9 An independent data monitoring and ethic committee (DMEC) will review the safety and ethics of the  
10 trial. Detailed reports will be prepared by the CTRU for the DMEC meetings which will take place at  
11 approximately yearly intervals. Additional reports will also be provided at intervals between these  
12 meetings. The committee will also review cumulative safety data by arm on an ongoing basis along  
13 with individual SAE/SAR listings. After each annual review, the DMEC will make their  
14 recommendations to the TSC about the continuation of the trial.  
15  
16

### 17 *Interim Analyses*

18  
19 Full interim reports will be presented to the DMEC in confidence annually and following the planned  
20 interim analyses which are expected to take place when half the number of events (119) have been  
21 observed in the treatment de-escalation pathway (R1) and at the end of the activity stage 1 treatment  
22 escalation pathway (R2), approximately 6 months after the 40<sup>th</sup> participant has been randomised.  
23  
24

25  
26 The interim analysis of R1 will be a one-sided test for inferiority conducted at the 5% significance level.  
27 PFS at R1 will be assessed using Cox proportional hazards regression to adjust for the minimisation  
28 factors (excluding centre), and presented using Kaplan-Meier estimates of the survival function.  
29  
30

31  
32 The interim analysis for R2 will be conducted at the end of Stage I (the phase II part) of the  
33 randomisation which is due 6 months following the randomisation of the 40<sup>th</sup> participant. This analysis  
34 will compare each experimental arm with the control arm in separate tests of superiority using a one-  
35 sided 25% significance level and 95% power to determine whether any of the experimental arms show  
36 lack of activity i.e. the null hypothesis in the superiority test is not rejected. Should an arm show lack  
37 of activity it will not be continued to the second stage of the randomisation (the phase III part). To  
38 account for the interim analysis and to give an overall significance level of 1% and power of 80% for  
39 each individual comparison the final analysis will be conducted using a one-sided 1% significance level  
40 and 85% power. Recruitment will continue seamlessly between activity and efficacy in these scenarios.  
41 Formal powered pair-wise comparisons are not undertaken comparing experimental arms at either  
42 stage.  
43  
44

45  
46 The DMEC committee members, in light of the interim analysis, will make their recommendations to  
47 the TSC about the continuation of the different aspects of the trial.  
48  
49

### 50 *Harms*

#### 51 Adverse events

52  
53 Adverse events are any untoward medical occurrence in a participant or clinical trial subject  
54 administered a medicinal product and which does not necessarily have a causal relationship with this  
55 treatment. AEs can be defined as any unintentional, unfavourable clinical signs or symptoms; any new  
56 illness or disease, or the deterioration of existing disease or illness; or clinically relevant deterioration  
57 in any laboratory assessments or clinical test. Due to the nature of multiple myeloma and its  
58  
59  
60

1  
2  
3 treatment, participants are likely to experience several adverse events throughout the course of the  
4 disease.  
5

6  
7 All AEs, both related and unrelated to myeloma treatment will be collected on the relevant eCRF from  
8 trial registration until 60 days after the last dose of protocol treatment and will be evaluated in  
9 accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events 5.0  
10 (NCI-CTCAE). AEs and ARs should continue to be collected for participants who are randomised to  
11 'stop isatuximab' at R1 (and until 60 days after last on-trial assessment), even though they will not be  
12 receiving any trial drugs during this period.  
13  
14

#### 15 16 Adverse Events of special interest

17 An AE of special interest (serious or non-serious) is one of scientific and medical concern specific to  
18 isatuximab, for which ongoing monitoring and rapid communication by the investigator to the sponsor  
19 is considered to be appropriate. Isatuximab AEs of special interest include;  $\geq$ Grade 3 infusion reactions  
20 (IRs), Pregnancies, Symptomatic overdoses with IMP, and Second Primary Malignancies (SPMs).  
21  
22

#### 23 24 Serious adverse events

25 Serious Adverse Events (SAEs) are defined as any untoward medical occurrence or effect that at any  
26 dose results in death; or are life threatening (at the time of the event); or require in-patient  
27 hospitalisation or prolongation of existing hospitalisation; or result in persistent or significant disability  
28 or incapacity; or result in a congenital anomaly or birth defect; or any other important medical event.  
29 All SAEs will be reported from registration until 60 days post the last dose of the trial drug. SAEs should  
30 continue to be collected for participants who are randomised to 'stop isatuximab' at R1 (and until 60  
31 days after last on-study assessment), even though they will not be receiving any study drugs during  
32 this period.  
33  
34  
35

36  
37 Serious Adverse Reactions (SARs) are SAEs that are deemed possibly related to any dose administered  
38 of any trial treatment. Suspected unexpected serious adverse events (SUSARs) are SARs which are not  
39 listed in the reference safety information for that medicinal product. SARs and SUSARs will be reported  
40 from the date of first trial dose and for the duration of the trial.  
41  
42

#### 43 44 Secondary malignancies

45 All new primary malignancies (SPMs) or suspected malignancies occurring from the date of trial  
46 registration and for the duration of the trial will be recorded. SPMs will be summarised and reviewed  
47 by an appointed member of the TMG who will determine whether trial treatment should continue.  
48  
49

#### 50 51 Pregnancies

52 Participants registered into RADAR agree to follow the Celgene approved Pregnancy Prevention  
53 Programme. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless  
54 of age or disease status) in a female participant must be reported throughout the study and for 12  
55 months after the last dose of cyclophosphamide or for 5 months following cessation of protocol  
56 treatment, whichever is longest. Pregnancies and suspected pregnancies (including a positive  
57 pregnancy test regardless of age or disease status) in a male participant's partner must be reported  
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3 throughout the study and for 6 months after the last dose of cyclophosphamide or for 5 months  
4 following cessation of protocol treatment, whichever is longest.  
5  
6  
7

### 8 *Safety Analyses*

9  
10 Safety analyses will summarise all SUSARs, SARs, SAEs, AEs and ARs, respective to where they occurred  
11 within the trial pathway (Induction, ASCT, Pre-R1, Post-R1, Post-R2, Post-R3). Safety data will be  
12 presented by treatment group for the safety population in addition to relationship to trial treatment.  
13  
14

### 15 *Auditing*

16 The CTRU and the trial sponsor have procedures in place to ensure that serious breaches of Good  
17 Clinical Practice (GCP) or the trial protocol are picked up and reported. A triggered monitoring plan  
18 will ensure that sites at risk are monitored accordingly.  
19  
20  
21

### 22 **Patient and Public Involvement**

23 RADAR has been developed following extensive discussion with the UK myeloma community. Patients  
24 were first involved into the research at the grant application stage, and were incorporated into the  
25 development of the primary endpoint of R1, in which they confirmed a research question involving  
26 the stopping of treatment given there was no detectable myeloma would be of interest. The trial  
27 consent and participant information documents were reviewed for clarity by a patient representative.  
28 To ensure that a patient perspective is considered throughout the trial a PPI advisory group, including  
29 4-8 members will feed into TMG meetings, and plan to host quarterly meetings to discuss urgent  
30 matters. It is envisioned that the PPI group, may help with writing summaries of results that can be  
31 published on patient forums and websites and maybe even shared directly with patients.  
32  
33  
34  
35  
36

### 37 **Ethics and Dissemination**

#### 38 **Research and ethics approval**

39  
40 Ethics approval has been obtained from the London – Central Research Ethics Committee  
41 (20/LO/0238). In addition capacity and capability has been confirmed by the appropriate research and  
42 development department for each participating centre prior to opening to participant recruitment  
43 into the trial. This included but was not limited to; having access to the non-trial supplied IMP (Bor, Cy  
44 and D), being able to conduct FISH as SoC, capacity of staff, ability to complete all protocol required  
45 assessments/investigations, and ability to archive trials documents.  
46  
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48

49 Participants will be required to provide informed consent before joining the trial.  
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#### 52 **Protocol Amendments**

53 The trial opened to recruitment on 11/05/2021 using protocol version 2, dated 29<sup>th</sup> April 2020. This  
54 publication is written based from protocol version 3 dated July 2021. An amendment to protocol  
55 version 3 is anticipated Mid-2022, which should include the following:  
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#### 59 *High-Risk Pathway*

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3 The cytogenetic abnormality del(1p) will be added to the definition of high-risk. In addition, Isa will be  
4 added to induction regimen for high-risk patients following their first cycle of RCyBorD (whilst their  
5 risk status is confirmed). Furthermore, R3 will be removed and high-risk patients will receive RBorIsaD  
6 + RIsa only post-ASCT. The pathway will follow a single-arm, single stage, phase II, three outcome  
7 design, with the new primary objective to assess the activity of RCyBorD+Isa induction followed by  
8 ASCT and RBorD+Isa consolidation and RIsa maintenance in terms of PFS at 18 months post trial  
9 registration.  
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#### 12 13 *Other changes*

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- 17 • The removal of the phone registration and randomisation;
- 18 • The clarification of allowing prescribed medication to remove risks of thromboembolism  
19 before preceding onto treatment in the exclusion criteria for registration (and for starting  
20 post ASCT treatment)
- 21 • An update of exclusion criteria to allow for previous plasmacytomas.  
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#### 24 25 **Consent or assent**

26 The PI retains overall responsibility for the informed consent of participants at their site and must  
27 ensure that any medically qualified person delegated responsibility to participate in the informed  
28 consent process is duly authorised, trained and competent to participate according to the ethically  
29 approved protocol, principles of GCP and Declaration of Helsinki. Written consent will be obtained  
30 and signed by a medically qualified member of the site research team. Informed consent must be  
31 obtained, and the participant must be registered into the trial prior to the participant undergoing  
32 procedures that are specifically for the purposes of the trial and are out-with standard routine care at  
33 the participating site. This include the confirmation of optional consent (QoL/ Healthcare resource use  
34 questionnaires and decision regarding consent for samples to be used in future research). At any  
35 stage, participants can withdraw consent without repercussion.  
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#### 40 41 **Confidentiality**

42 All information collected during the course of the trial will be kept strictly confidential. Information  
43 will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU  
44 will comply with all aspects of the Data Protection Act 2018.  
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#### 47 48 **Access to data**

49 The CTRU will control the final trial datasets, and any requests for data will be reviewed by the trial  
50 management group in the first instance. Only requests that have a methodologically sound proposal  
51 and whose proposed use of the data has been approved by the independent trial steering committee,  
52 based on the principles of a controlled access approach, and subject to existing contractual  
53 agreements with the funder, will be considered. Proposals should be directed to the corresponding  
54 author in the first instance; to gain access, data requestors will need to sign a data access agreement.  
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### **Ancillary and post-trial agreements**

Participants who stop trial treatment due to progression or any point prior to the end of trial will be treated off-trial at the discretion of their treating clinician. Those who stop prior to disease progression will be followed up 2 monthly until disease progression, death or the end of the trial. Following disease progression all participants will be followed up annually until death, or until the end of the trial for post progression endpoints.

Participants in the R1 pathway who are MRD-positive at 12 months post 12 cycles of isatuximab and therefore aren't eligible for randomisation 1 will continue to receive isatuximab maintenance, these participants would continue to be monitored, and data collected, as previously but trial samples would not be collected.

### **Dissemination policy**

Authorship will be in keeping with the UK-MRA publication policy and due acknowledgement to participants, local investigators, funders and NCRI Haematological Oncology Study Group support made. The success of the trial depends upon the collaboration of all participants. For this reason, credit for the main results will be given to all those who have collaborated in the trial, through authorship and contributor-ship. Uniform requirements for authorship for manuscripts submitted to medical journals will guide authorship decisions alongside the guidance of the UK Myeloma Research Alliance Authorship Policy.

To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial or a primary endpoint being reached, either for trial publication or oral presentation purposes, without the permission of the Trial Steering Committee and the (Co-)Chief Investigators. In addition, individual collaborators must not publish data concerning their participants that is directly relevant to the questions posed in the trial until the main results of the trial have been published and following written consent from the Sponsor.

### **Appendices**

#### *Informed consent material*

The consent forms which are to be completed by the participant at Bone Marrow Registration and/or Trial Registration and prior to each randomisation pathways are included in supplementary material.

#### *Biological specimens*

The collection of central samples for laboratory analysis is summarised in Figures 3 and 4. The analysis to be conducted for trial purposes is stated in the supplementary material. Additional analysis may be carried out by each central laboratory provided the appropriate consent for sample use in future research has been provided by the participant at trial entry.

### **Author Contributions**

The RADAR trial was conceived by KY and MC and designed by them in collaboration with DAC. All authors inputted into the development of the protocol and participant information sheet. The first

1  
2  
3 draft of the protocol paper was written by KLR and ABC. All authors reviewed and approved the final  
4 manuscript.  
5

### 6 7 **Funding**

8 This trial is funded by Cancer Research UK, Sanofi Genzyme and Celgene: A BMS Company. The funders  
9 had no role in the design, collection, analysis or collection of data; in writing the manuscript; or in the  
10 decision to submit the manuscript for publication.  
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14 The trial sponsor is responsible for the overall conduct of the trial as defined by Directive 2001/20/EC  
15 is University of Leeds, UoL/LTHT Joint Sponsor QA office (CTIMPs); Research & Innovation  
16 Centre/Faculty of Medicine & Health; Leeds Teaching Hospitals NHS Trust/University of Leeds; St  
17 James University Hospital; Leeds LS9 7TF.  
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### 19 20 21 **Competing Interest Statement**

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23 ABC, KLR, DAC, AH, CO, LBai, LBar, AP, RL report grants and non-financial support from BMS/Celgene,  
24 grants and non-financial support from Merck Sharpe & Dohme, grants and non-financial support from  
25 Amgen, grants and non-financial support from Takeda, during the conduct of the trial. DAC also  
26 reports travel support from Celgene Corporation.  
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30 KY, RDT, CB, GJ, GP, MC, BD, DM, GC, HA, KR,SA, AC have no conflicting interests to declare. MC  
31 declares, Bristol Myers Squibb- employee, Honoraria/travel support in the last 3 years from, Amgen  
32 ,BMS/Celgene, Janssen, Takeda, Abbvie. CP declares BMS/Celgene Ad boards and speaker fees, Sanotif  
33 – Ad board, speaker fees, conference registration fees. JS reports Carrying out consultancy work  
34 (Advisory Board) for Sanofi. And an educational speaking engagement for Celgene/BMS RP declares;  
35 Honoraria – Janssen, BMS, Abbvie, GSK. Consultancy: GSK, Janssen. Meeting support: Janssen,  
36 Takeda, BMS. RO declares- Janssen - advisory board, honoraria, Celgene – honoraria, Beigene -  
37 advisory board, honoraria, Astra Zeneca – honoraria. MK declares inter-relationships: AbbVie:  
38 consultancy; Amgen: honoraria; BMS/Celgene: consultancy, research funding (institution); GSK:  
39 consultancy; Janssen: consultancy, research funding (institution); Karyopharm: consultancy; Pfizer:  
40 consultancy; SeattleGenetics: consultancy; Takeda: consultancy; Sanofi: honoraria. MD reports  
41 owning stock in Abingdon Health. SQ is the founder and CSO of Achilles therapeutics a company  
42 developing T cell therapies for solid tumours.  
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3 **Figure Legends/ Captions**

4 Figure 1: Flow chart of participant's timelines in the RADAR study

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6 Figure 2: Schedule of local investigations

7 Figure 3: Central Investigations from diagnosis up to 100 days post-ASCT

8 Figure 4: Central Investigations for the R1, R2 and R3 pathways  
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For peer review only

Figure 1: Flowchart of Participants timelines in the RADAR Study

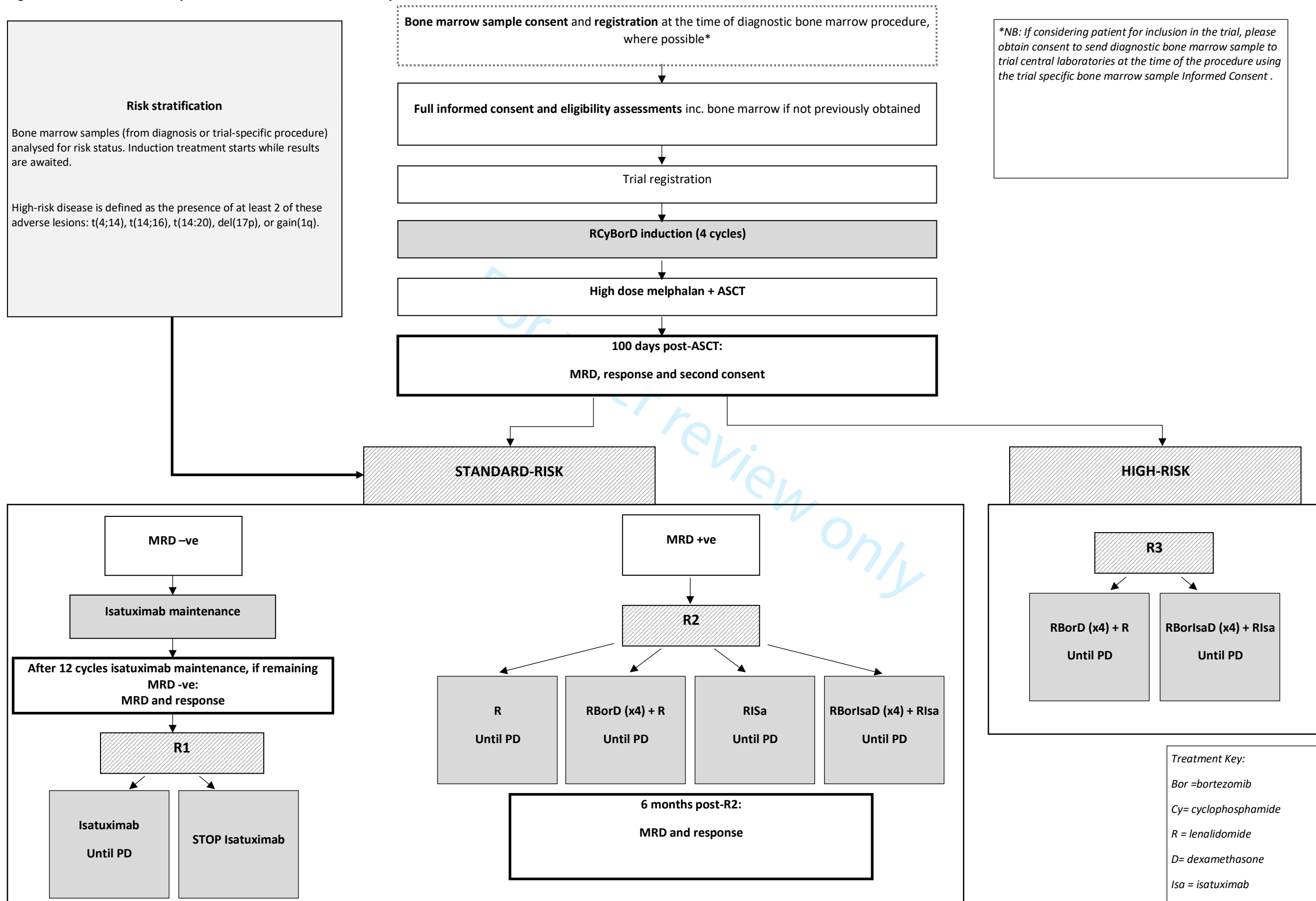


Figure 2: Schedule of Local Investigations

	RCyBorD Induction – All participants				R1 treatment pathway			R2 and R3 treatment pathway R2 participants on R or R1sa arm: After 3,6,12 and 18 cycles**		
	Pre-registration/baseline (within 14 days prior to registration, unless otherwise stated)	Day 1 (or day -1) of each cycle during RCyBorD induction††	End of RCyBorD induction	100 days post-ASCT (within 14 days prior to R2, start of Isatuximab maintenance or R3)	Day 1 of each cycle of isatuximab treatment††	On the day of isatuximab dose††	Follow up for participants coming off study during R1 treatment pathway: every 2 months	Day 1 of each cycle of treatment††	On day of (and prior to) every isatuximab dose††	Follow up for participants coming off study during R2/R3 treatment pathway: every 2 months
Written informed consent	✓ Consent to be taken prior to all assessments, permitted outside the 14-day window			✓ (permitted outside the 14-day window)						
Physical examination	✓	✓	✓	✓	✓			✓		
ECOG	✓	✓	✓	✓	✓			✓		
Covid vaccination status	✓	✓	✓	✓	✓		✓	✓		✓
Medical history (including review for prior cancers and history of Covid infection)	✓		✓	✓						
Assessment of cardiac risk*	✓(results from formal measurements within 28 days prior to registration)	If clinically indicated	✓	If clinically indicated	If clinically indicated			If clinically indicated		
ECG					Every 3 months in participants receiving Isatuximab			Every 3 months in participants receiving Isatuximab		
Thyroid function monitoring*	✓(within 28 days prior to registration)	If clinically indicated	✓	If clinically indicated	If clinically indicated			If clinically indicated		
FBC, LFTs, albumin, LDH, U&Es, calcium, and creatinine¶	✓	✓	✓	✓	✓	✓ FBC, U&E and creatinine only		✓	✓ FBC, U&E and creatinine only	
Hepatitis B, (surface antigen and core antibody), ,hepatitis C and HIV	⊠(within 28 days prior to registration)									
β2-microglobulin (β2M)	✓									
C-Reactive protein (CRP)	✓									
Calculated creatinine clearance (using Cockcroft-Gault formula)	✓	✓	✓	✓	✓			✓		
Serum paraprotein and immunofixation, serum free light chains and urinary free light chain detection	✓	✓	✓	✓	✓		✓ (if performed as part of standard care)	✓		✓ (If performed as standard of care)
Bone marrow (aspirate and trephine) See Table below for details of central investigations	✓ (within 6 weeks prior to registration)	✓(recommended only if a first occurrence of CR or sCR is suspected)	✓	✓	✓(recommended only if a first occurrence of CR or sCR is suspected)		✓ (if performed as part of standard care)	✓ (recommended only if first occurrence of CR/sCR is suspected)		✓ (If performed as standard of care)
Pregnancy prevention counselling	✓	At least every 28 days during lenalidomide treatment								
Pregnancy test† (for females of childbearing potential)	✓	✓‡			✓				✓‡	
Cross-sectional imaging according to local practice, to include the thorax (low dose whole body CT recommended)	Within 3 months before registration§	If clinically indicated. †			If clinically indicated			If clinically indicated		
Assessment of adverse events (including adverse events and second primary malignancy)		Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose)			Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose) . AEs should continue to be monitored for participants randomised to ‘stop Isatuximab’ at R1 (and until 60 days after last on-study assessment).			Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose)		

\*Performed as part of standard of care.  
 \*\* ECGs should be scheduled to align with other required face-to-face visits  
 ¶ The FBC should be repeated mid-cycle 1 (Day 14 +/-3 days) or more frequently and during subsequent cycles if there is a concern about cytopenias  
 † Females of childbearing potential (FCBP) must have a negative pregnancy test performed by a healthcare professional in accordance with the Celgene Lenalidomide Pregnancy Prevention Plan  
 †† May be performed within the 48 hours prior to the specified day  
 ††† In addition to standard Day 1 assessments  
 ‡ All FCBP: The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide.  
 FCBP with regular or no menstrual cycles: within 24 hours before start of lenalidomide treatment; weekly for the first 28 days of study participation; 4-weekly as a minimum during lenalidomide treatment; at study discontinuation; and 4 weeks after last dose of lenalidomide  
 FCBP with irregular menstrual cycles: within 24 hours before start of lenalidomide treatment; weekly for the first 28 days of study participation; 2-weekly as a minimum during lenalidomide treatment; at study discontinuation; and at 2 and 4 weeks after last dose of lenalidomide

**N.B. During the COVID-19 pandemic, face-to-face assessments must be carried out at least at the beginning of cycles 1 and 2 and at the end of consolidation. Subsequently, participants must be seen by a clinician at least every 3 cycles (and more frequently if clinically indicated or there are concerns).**



Figure 3: Central Investigations from diagnosis up to 100 days post-ASCT

Sample	Investigation	Diagnosis (if patient consented on NHS form and trial bone marrow Informed Consent Document) <sup>1</sup>	Baseline (post trial consent and before the start of treatment)	Day 1 of Cycle 1 RCyBorD induction	End of induction cycle 1	End of induction cycle 2	End of RCyBorD induction	100 days post-ASCT and prior to consolidation/maintenance
0.5-1 mL EDTA bone marrow aspirate <b>SEND TO HMDS, LEEDS</b>	Minimal Residual Disease	✓	✓ (if not sent previously)				✓	✓
10 mL clotted peripheral blood Random urine sample <b>SEND TO BIRMINGHAM</b>	Disease parameters (including paraproteins) for response assessments and covid-19 antibody response M-protein interference assay		✓	✓ Only if baseline sample not within 14 days	✓	✓	✓	✓
10 mL EDTA bone marrow aspirate 10 mL blood <b>SEND TO UCL, LONDON</b>	Tumour DNA for neoantigens cfDNA Immune profiling	✓ Bone marrow only	✓ BMA (if not sent previously) & blood	✓ Cycle 1 only 10 mL blood (only if baseline sample is not from within 14 days prior to cycle 1 day 1)				✓
Bone marrow trephine (6 sections) <b>SEND TO UCL, LONDON</b>	Immunostaining for immune function	✓	✓ (if not sent previously)					✓

Trial consent  
Consented to Myeloma XV trial and central laboratory investigations

<sup>1</sup> Baseline bone marrow samples may be taken before trial consent, provided that patients have consented to these samples being taken using the standard NHS consent form. The patient must have provided written informed trial consent on the trial bone marrow Informed Consent Document before these samples can be sent to the central laboratories.

Figure 4: Central Investigations for the R1, R2 and R3 pathways

Sample	Investigation	Standard-risk MRD-negative participants (R1 pathway)	Standard-risk MRD-positive participants on R or R1sa arm (R2 pathway)			Standard-risk MRD-positive participants on RBorD+R or RBor1saD+R1sa arm (R2 pathway)			High-risk participants (R3 pathway)			All participants
			After cycle 3	After cycles 6, 12 and 18	After cycle 24	After consolidation cycle 4	After maintenance cycles 3, 9 and 15	After maintenance cycle 21	After consolidation cycle 4	After maintenance cycles 3, 9 and 15	After maintenance cycle 21	
		After cycles 6, 12 and 24 of maintenance (or at equivalent time-points if randomised to stop receiving 1sa)										Disease progression
0.5-1 mL EDTA bone marrow aspirate SEND TO HMDS, LEEDS	Minimal Residual Disease	✓	✓	✓		✓	✓		✓	✓		✓
10 mL clotted peripheral blood Random urine sample SEND TO BIRMINGHAM	Disease parameters (including paraproteins) for response assessments and covid-19 antibody response M-protein interference assay	✓	✓	✓	✓ (blood only)	✓	✓	✓ (blood only)	✓	✓	✓ (blood only)	✓
10 mL EDTA bone marrow aspirate 10 mL blood SEND TO UCL, LONDON	Tumour DNA for neoantigens cfDNA Immune profiling	✓ (only after 6 cycles)	✓			✓			✓			✓
Bone marrow trephine SEND TO UCL, LONDON	Immuno-chemistry for immune function		✓			✓			✓			✓

## **RADAR: Protocol Paper Attachments**

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## 1 Glossary of Terms

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6	AE	Adverse event
7	ALT	Alanine aminotransferase
8	ANC	Absolute neutrophil count
9	AR	Adverse reaction
10	ASCT	Autologous stem cell transplantation
11	β2M	Beta2-microglobulin
12	BD	Twice daily
13	CI	Chief Investigator
14	CR	Complete response
15	CRF	Case report form
16	CRUK	Cancer Research United Kingdom
17	CTCAE	Common Terminology Criteria for Adverse Events
18	CTRU	Clinical Trials Research Unit
19	Cy	Cyclophosphamide
20	D	Dexamethasone
21	DMEC	Data Monitoring and Ethics Committee
22	DSUR	Developmental Safety Update Report
23	ECOG	Eastern Cooperative Oncology Group
24	eCRF	Electronic Case Report Form
25	EORTC	European Organisation for Research and Treatment of Cancer
26	FISH	Fluorescence in situ hybridization test
27	FWER	Family-wise error rate
28	GCP	Good Clinical Practice
29	HDM	High-dose melphalan
30	HMDS	Haematological Malignancy Diagnostic Service
31	IMiD®	Immunomodulatory Drug
32	IMP	Investigational medicinal product
33	IMWG	International Myeloma Working Group
34	IPD	Individual participant data
35	Isa	Isatuximab
36	ISS	International Staging System
37	ITT	Intention to treat
38	LFT	Liver function test
39	MedDRA	Medical Dictionary for Regulatory Activities
40	mg	Milligram
41	MGUS	Monoclonal gammopathy of undetermined significance
42	MHRA	Medicines and Healthcare Products Regulatory Agency
43	MM	Multiple myeloma
44	MR	Minimal response
45	MRD	Minimal Residual Disease
46	NCRI	National Cancer Research Institute
47	NDMM	Newly diagnosed multiple myeloma
48	NICE	National Institute for Health and Care Excellence
49	OS	Overall survival
50	PD	Progressive disease
51	PFS	Progression-free survival
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3	PFS2	Time to second progression
4	PI	Principal Investigator
5	PIS	Patient Information Sheet
6	PP	Paraprotein
7	PR	Partial response
8	PS	Performance status
9	QoL	Quality of life
10	R	Lenalidomide
11	R1-3	Randomisation 1-3
12	RCT	Randomised controlled trials
13	RDE	Remote Data Entry
14	REC	Research Ethics Committee
15	R-ISS	Revised International Staging System
16	RSI	Reference Safety Information
17	SC	Sub-cutaneous
18	SD	Stable disease
19	SAE	Serious adverse event
20	SAP	Statistical analysis plan
21	SAR	Serious adverse reaction
22	SmPC	Summary of Product Characteristics
23	SOP	Standard operating procedure
24	SPM	Secondary Primary Malignancy
25	SSOP	Study site operating procedure
26	SUSAR	Suspected unexpected serious adverse reaction
27	TE	Transplant eligible
28	TMG	Trial Management Group
29	TNE	Transplant non-eligible
30	TSC	Trial Steering Committee
31	U&Es	Urea & electrolytes
32	UK-MRA	United Kingdom Myeloma Research Alliance
33	ULN	Upper limit of normal
34	VGPR	Very good partial response
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## 2 List of Sites in the RADAR Trial

Aberdeen Royal Infirmary	Royal Bournemouth Hospital	University Hospital Wishaw
Royal Sussex County Hospital	Poole General Hospital	St Richard's Hospital
Chesterfield Royal Hospital	Salisbury District Hospital	Worthing Hospital
Derriford Hospital	Sunderland Royal Hospital	The Christie
Kent & Canterbury Hospital, Canterbury	South Tyneside District Hospital	Cheltenham General Hospital
Queen Elizabeth the Queen Mother Hospital	Southmead Hospital Bristol	Gloucestershire Royal Hospital
William Harvey Hospital	St. Helens	The Clatterbridge Centre
Freeman Hospital	Whiston Hospital	
Queen Elizabeth Hospital Gateshead	St George's Hospital (Tooting)	
Hammersmith Hospital	Torbay Hospital	
Manchester Royal Infirmary	University College London Hospital	
Wythenshawe Hospital	Leicester Royal Infirmary	
Milton Keynes University Hospital	Worcestershire Royal Hospital	
Perth Royal Infirmary	Alexandra Hospital, Redditch	
Ninewells Hospital	York Hospital	
Northampton General Hospital	University Hospital of Wales, Cardiff	
Churchill Hospital	Stratford Hospital	
Horton General Hospital	Warwick Hospital	
Queen Alexandra Hospital, Portsmouth	New Cross Hospital	
Queen Elizabeth Hospital, Birmingham	University Hospital Coventry	
Raigmore Hospital, Inverness	University Hospital Monklands	
Rotherham General Hospital	University Hospital Hairmyres	

### 3 Spirit Checklist: Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	1,2,3
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	<a href="#">#3</a>	Date and version identifier	29
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	32
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1, 31
Roles and responsibilities: sponsor contact information	<a href="#">#5b</a>	Name and contact information for the trial sponsor	31,32
Roles and responsibilities: sponsor and funder	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	32
Roles and responsibilities: committees	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	26,27
<b>Introduction</b>			
Background and rationale	<a href="#">#6a</a>	Description of research question and justification for undertaking the trial, including summary of relevant	6,7

		studies (published and unpublished) examining benefits and harms for each intervention	
Background and rationale: choice of comparators	<a href="#">#6b</a>	Explanation for choice of comparators	6,7
Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7, 18
Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	8
<b>Methods:</b>			
<b>Participants, interventions, and outcomes</b>			
Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8-14
Interventions: description	<a href="#">#11a</a>	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	15-17
Interventions: modifications	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	17
Interventions: adherence	<a href="#">#11c</a>	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	17
Interventions: concomitant care	<a href="#">#11d</a>	Relevant concomitant care and interventions that are permitted or prohibited during the trial	17
Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	18



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2				
3	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18,19
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8	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
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13	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	23
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17	<b>Methods:</b>			
18	<b>Assignment of</b>			
19	<b>interventions (for</b>			
20	<b>controlled trials)</b>			
21				
22	Allocation: sequence generation	<a href="#">#16a</a>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	23
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31	Allocation concealment mechanism	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	23
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37	Allocation: implementation	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	23
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
42				
43				
44				
45	Blinding (masking): emergency unblinding	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
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50	<b>Methods: Data</b>			
51	<b>collection,</b>			
52	<b>management, and</b>			
53	<b>analysis</b>			
54				
55	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires,	23
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		laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
7	Data collection plan: retention	<a href="#">#18b</a> Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	23
12	Data management	<a href="#">#19</a> Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	23
20	Statistics: outcomes	<a href="#">#20a</a> Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
26	Statistics: additional analyses	<a href="#">#20b</a> Methods for any additional analyses (eg, subgroup and adjusted analyses)	24
29	Statistics: analysis population and missing data	<a href="#">#20c</a> Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	24
34	<b>Methods:</b>		
35	<b>Monitoring</b>		
37	Data monitoring: formal committee	<a href="#">#21a</a> Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	27
46	Data monitoring: interim analysis	<a href="#">#21b</a> Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	27
52	Harms	<a href="#">#22</a> Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	27
57	Auditing	<a href="#">#23</a> Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	29

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3	<b>Ethics and</b>			
4	<b>dissemination</b>			
5				
6	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee /	29
7	approval		institutional review board (REC / IRB) approval	
8				
9	Protocol	<a href="#">#25</a>	Plans for communicating important protocol	29
10	amendments		modifications (eg, changes to eligibility criteria,	
11			outcomes, analyses) to relevant parties (eg,	
12			investigators, REC / IRBs, trial participants, trial	
13			registries, journals, regulators)	
14				
15	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from	30
16			potential trial participants or authorised surrogates,	
17			and how (see Item 32)	
18				
19				
20	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	30,31
21	ancillary studies		participant data and biological specimens in ancillary	
22			studies, if applicable	
23				
24	Confidentiality	<a href="#">#27</a>	How personal information about potential and	30
25			enrolled participants will be collected, shared, and	
26			maintained in order to protect confidentiality before,	
27			during, and after the trial	
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29				
30	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	32
31	interests		investigators for the overall trial and each study site	
32				
33	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial	30
34			dataset, and disclosure of contractual agreements that	
35			limit such access for investigators	
36				
37	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and	32
38	trial care		for compensation to those who suffer harm from trial	
39			participation	
40				
41	Dissemination	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate	31
42	policy: trial results		trial results to participants, healthcare professionals,	
43			the public, and other relevant groups (eg, via	
44			publication, reporting in results databases, or other	
45			data sharing arrangements), including any publication	
46			restrictions	
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49	Dissemination	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use	31
50	policy: authorship		of professional writers	
51				
52	Dissemination	<a href="#">#31c</a>	Plans, if any, for granting public access to the full	31
53	policy: reproducible		protocol, participant-level dataset, and statistical code	
54	research			
55				
56	<b>Appendices</b>			
57				
58	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation	(Supplementary
59	materials		given to participants and authorised surrogates	Material)
60				

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3 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage (Supplementary  
4 of biological specimens for genetic or molecular Material)  
5 analysis in the current trial and for future use in  
6 ancillary studies, if applicable  
7

8 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative  
9 Commons Attribution License CC-BY-NC. This checklist can be completed online using  
10 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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#### 4 Excluded Concomitant Medication:

##### Excluded concomitant Medication:

1. Systemic treatment with any of the following metabolising enzyme inducers and inhibitors should be avoided, unless there is no appropriate alternative medication for the participant's use (if there were to be a drug-drug interaction with an inducer, cyclophosphamide and bortezomib metabolite exposure would be increased):
  - a. Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
  - b. Strong CYP3A inhibitors
2. Excluded foods and dietary supplements include St. John's Wort, green tea and supplements containing green tea extracts
3. The following medicinal products and procedures are **prohibited** during this study:
  - a. Any antineoplastic treatment with activity against MM, other than study drugs
  - b. Platelet transfusions within 3 days prior to study drug dosing for any dosing day, or prior to randomisation in order to meet eligibility criteria.
  - c. Additional steroid therapy (not as trial IMP) (except before commencing trial treatment up to a maximum of 160mg dexamethasone equivalent as per inclusion criteria or steroids used to manage hypersensitivity to trial medication)
  - d. Radiotherapy for the treatment of symptoms related to disease progression.
  - e. Continuous use of clarithromycin (short courses of 5-10 days are permitted for treatment of infective episodes when indicated)
  - f. Hormone replacement therapy and erythropoietic agents and other agents that increase the risk of thrombosis (applicable during treatment with lenalidomide)

## Quality of Life and Health Economics questionnaires

### Timepoints for all participants up to 100 days post-ASCT

- Baseline
- End of induction
- 100 days post-ASCT

### \*R1 pathway participants

- After cycles 6, 12, 24 and 36 (for participants randomised to 'stop isatuximab' at R1, the cycle 24 and 36 questionnaires should still be completed at equivalent timepoints)

### \*Timepoints for R2 and R3 pathway participants receiving R or RIsa

- After cycles 6, 12 and 24 of maintenance

### \*Timepoints for R2 and R3 pathway participants receiving RBorD+R or RBorIsaD+RIsa

- After cycles 3, 9 and 21 of maintenance.

*\*Note that participants who stop trial treatment should complete QoL at the equivalent time points (unless the participant wishes to withdraw consent for any further data collection)*

## 5 Exploratory analysis

Exploratory analysis will consider; the effect of post-ASCT consolidation regimens utilising combinations of lenalidomide, bortezomib, dexamethasone, and isatuximab on immune function in the bone marrow of participants following ASCT, using high dimensional characterisation of the immune microenvironment, immune subsets, phenotype and transcriptome; T cell receptor (TCR) repertoire in the bone marrow of participants following ASCT and consolidation and/or maintenance; correlation of baseline immune profile, TCR diversity and function with disease response, including MRD status and timing of disease relapse; ex-vivo functional studies with participant derived samples used to generate explants or immune-competent patient derived xenografts (icPDX); and to review infection and re-infection rates of COVID-19 in participants during induction, post-ASCT and during post-ASCT consolidation and maintenance treatment. All exploratory analysis to be conducted by the trial statisticians will be pre-specified in the statistical analysis plan.

## 6 Subgroup analysis

Subgroup analysis will be conducted to determine whether a selection of patient characteristics, haematology / local serological results, biochemistry results and cytogenetic/molecular results as well as response assessments (full list below) are prognostic of the endpoints; PFS, PFS2, OS, attainment of  $\geq$ VGPR and attainment of MRD negativity, as defined for all randomisations. Note that the subgroups listed under the Response subheading will not be analysed for the last two endpoints.

### Patient Characteristics

- Age (years) at trial registration ( $\leq 65$ ,  $>65$ )
- Sex (Male / Female)
- ECOG performance status at trial registration (0, 1,  $\geq 2$ )
- ISS at trial registration (Stage I, Stage II, Stage III)
- R-ISS at trial registration (Stage I, Stage II, Stage III)

### Haematology / Local Serological Results

- Haemoglobin concentration at trial registration ( $<100$ ,  $\geq 100$  g/L)
- Platelets at trial registration ( $<150$ ,  $\geq 150 \times 10^9$ /L)
- White blood cells at trial registration ( $< LLN$  (Lower limit of normal),  $\geq LLN$ )
- Neutrophil count at trial registration ( $< LLN$ ,  $\geq LLN$ )
- Lymphocyte count at trial registration ( $< LLN$ ,  $\geq LLN$ )
- Plasma cells (%) in bone marrow at trial registration ( $<60\%$ ,  $\geq 60\%$ )

### Biochemistry Results

- $\beta$ -2 microglobulin concentration at trial registration ( $<3.5$ ,  $3.5$ – $<5.5$ ,  $\geq 5.5$  mg/L)
- Serum creatinine concentration at trial registration ( $<175$ ,  $\geq 175$   $\mu$ mol/L)
- Corrected serum calcium concentration at trial registration ( $<2.75$ ,  $\geq 2.75$  mmol/L)
- Serum albumin at trial registration ( $<ULN$  (Upper limit of normal),  $\geq ULN$ )
- Lactate dehydrogenase at trial registration ( $<ULN$ ,  $\geq ULN$ )
- C-Reactive protein at trial registration ( $<ULN$ ,  $\geq ULN$ )
- Serum bilirubin at trial registration ( $<ULN$ ,  $\geq ULN$ )
- ALT/AST at trial registration ( $<ULN$ ,  $\geq ULN$ )

### Cytogenetic/molecular Results

- t(4,14) at trial registration (detected, not detected)
- t(14,16) at trial registration (detected, not detected)
- t(14,20) at trial registration (detected, not detected)
- del(17p) at trial registration (detected, not detected)
- 1q gain at trial registration (detected, not detected)
- Hyperdiploidy at trial registration (detected, not detected)
- The number of high-risk adverse lesions at trial registration (R1 and R2: 0, 1 unable to determine, R3: 2,  $\geq 3$ , or unable to determine)

### Response



- Response to RCyBorD induction (<VGPR, ≥ VGPR)
- Response at 100 days post-ASCT (<VGPR, ≥ VGPR)
- Response at the end of consolidation (<VGPR, ≥ VGPR)
- Response to 12m post-ASCT treatment (<VGPR, ≥ VGPR)
- MRD response to RCyBorD induction (R3 Only: MRD positive, MRD Negative)
- MRD at 100 days post-ASCT (R3 Only: MRD positive, MRD negative)
- MRD response to 6m post-ASCT treatment (R3 Only: MRD positive, MRD Negative)
- MRD response to 12m post-ASCT treatment (R3 Only MRD positive, MRD Negative)

Further subgroup analyses may be undertaken, as appropriate and all the subgroups will be fully defined within the statistical analysis plan according to the current criteria [1-3].

For peer review only

**7 Informed Consent Material**

Bone Marrow Consent

**Delete this line, then print on Trust/Hospital headed paper**

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number :
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)**

**INFORMED CONSENT DOCUMENT FOR BONE MARROW AND BLOOD SAMPLE**

**Please initial each box**

1. I confirm that I have read and understand the information sheet for the bone marrow sample request and have had the opportunity to ask questions.
2. I understand that my providing bone marrow samples is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected.
3. I understand that the samples will be sent along with information about me, which will include NHS number or CHI number for Scotland and may include my name.
4. I agree to these samples being stored and used for research investigations that form part of the RADAR study, and understand that this will include genetic research (for example, analysis of DNA).

- 5. I understand that a unique reference number will be allocated to the samples which may allow them to be linked back to me in future for research purposes.
- 6. I understand that my data may be shared on a collaborative basis with researchers in the UK and potentially, centres abroad.
- 7. I agree to allow any information provided to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible.
- 8. I understand that results of my laboratory tests may be shared with other research teams if I am taking part in another clinical study being run by the University of Leeds.
- 9. I agree to a copy of this Consent Form being sent to the Clinical Trials Research Unit.
- 10. I agree for my details (which will include date of birth and NHS number or CHI number for Scotland) to be submitted to NHS Digital or other central UK NHS bodies so that information about my health, and mortality should this become available, may be obtained by the CTRU if necessary.
- 11. I agree to provide bone marrow samples.

**Please indicate your wishes in the below scenarios:**

A) If I am diagnosed with a plasma cell dyscrasia, other than myeloma, I give permission for the samples sent to the central laboratories to be stored and used in future research that receives ethical approval. I understand that the samples and data collected from them may be shared with researchers, possibly in other countries.

**Please initial**

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

B) If I am diagnosed with myeloma but do not take part in the RADAR study, I give permission for the samples sent to the central laboratories to be stored and used in future research that receives ethical approval. I understand that the samples and data collected from them may be shared with researchers, possibly outside the EEA.

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

**Patient (to be completed by the patient):**

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the request to the above named patient and he/she has indicated his/her willingness for samples of bone marrow to be sent to the RADAR laboratories.

Signature.....

Name (block capitals).....

Date.....

**(If used)Translator:**

Signature.....

Name (block capitals).....

Date.....

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

For peer review only

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## Part A: Initial Treatment and Further Study Consent

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



## RADAR (UK-MRA Myeloma XV)

### INFORMED CONSENT DOCUMENT PART A

#### Initial Treatment and Further Study Information

PLEASE INITIAL  
EACH BOX

12. I confirm that I have read and understand the Part A information document for the RADAR study and have had the opportunity to ask questions.
13. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. I understand that even if I withdraw from the above study, the data and samples collected from me will be used in analysing the results of the study, and in some cases further information about any unwanted effects of my treatment may need to be collected by the study team.
14. I understand that my healthcare records may be looked at by authorised individuals from the study team, regulatory bodies or Sponsor in order to check that the study is being carried out correctly.
15. I am aware that I am required to have samples taken and sent to laboratories and I understand that this will include genetic research (for example, analysis of DNA). I understand that the samples will be sent along with information about me, which will include NHS number, or CHI number for Scotland, and may include my name.

- 16. I understand that results or reports from imaging scans, blood tests or other investigations (including for additional cancers) may be sent to the Clinical Trials Research Unit for central review by the research team.
- 17. I agree to allow any information or results arising from this study to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible.
- 18. I understand that my data and results of my laboratory tests (blood, urine and bone marrow sample collections) may be shared with other research teams if I am taking part in another clinical study being run by the University of Leeds.
- 19. I agree for my details (which will include date of birth and NHS number or CHI number for Scotland) to be submitted to NHS Digital or other central UK NHS bodies so that information about my health may be obtained by the CTRU if necessary.
- 20. I understand that my GP, or any other doctor treating me, will be notified of my participation in this study.
- 21. I understand that some of my data may be passed to other organisations, such as the pharmaceutical companies Sanofi and Celgene, (possibly in other countries where the data protection standards and laws may be different from the UK) to monitor the safety of the treatment(s) that I am receiving. I understand that my identity will remain anonymous.
- 22. I agree to a copy of this Consent Form being sent to the Clinical Trials Research Unit.
- 23. I agree to take part in the study.

**The following parts of the study are OPTIONAL (see section 3 of the Participant Information Sheet).** Even if you agree to take part in the RADAR study, you do not have to agree to these optional parts. Please initial yes or no.

Please initial

A) I agree to take part in the Quality of Life and Healthcare Resource Use studies by completing questionnaires at timepoints throughout the study. Yes  No

B) I give permission for samples that I provide to be used in future research that receives ethical approval, and I understand that this includes the bone marrow samples provided at the time of my diagnosis (if I consented separately to collection of the diagnostic bone marrow sample in anticipation of participation in this study). I understand that my samples and data collected from them may be shared on a collaborative basis with researchers in the UK and, potentially, centres abroad. Yes  No

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

Date.....

(If used) Translator:

Signature.....

Name (block capitals).....

Date.....

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

For peer review only

Part B: Randomisation 1 Treatment Group

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)**  
**INFORMED CONSENT DOCUMENT PART B**  
**R1 Treatment Group**

PLEASE INITIAL  
EACH BOX

24. I confirm that I have read and understand the Part B information document for the RADAR study and have had the opportunity to ask questions.

25. I agree to continue my participation in the study as part of the R1 Treatment Group.

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

Date.....



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(If used) Translator:

Signature.....

Name (block capitals).....

Date.....

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

For peer review only

Part C: Randomisation 2 Treatment Group

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)**  
**INFORMED CONSENT DOCUMENT PART C**  
**R2 Treatment Group**

**PLEASE INITIAL EACH BOX**

26.I confirm that I have read and understand the Part C information sheet for the RADAR study and have had the opportunity to ask questions.

27.I agree to continue my participation in the study as part of the R2 Treatment Group.

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

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(If used) Translator:

Signature.....

Name (block capitals).....

Date.....

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

For peer review only

Part D: Randomisation 3 Treatment Group

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)**  
**INFORMED CONSENT DOCUMENT PART D**  
**R3 Treatment Group**

PLEASE INITIAL  
EACH BOX

28. I confirm that I have read and understand the Part D information sheet for the RADAR study and have had the opportunity to ask questions.

29. I agree to continue my participation in the study as part of the R3 Treatment Group.

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

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Signature.....

Name (block capitals).....

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(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

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## 8 Central Sample Analysis

The trial has 3 central laboratories receiving samples for trial purposes. The time points and the reason for analysis for each central sample can be found in Figure 2. Details on the analysis of each sample is below. Note that participants can consent for their samples to be used in future research and hence each laboratory can store their trial samples for use in future studies. The storage details are also included below.

### Birmingham

The Birmingham University Clinical Immunology Laboratory holds UKAS ISO 15189:2012 - Medical Laboratories accreditation. The Trial-related Laboratory Work will be performed using standard assays to the same quality standard as during routine clinical care. The Laboratory will be responsible for the analysis of whole clotted blood, serum and urine collected from participants of the Research Project in accordance with the Protocol. The laboratory will measure disease response and Disease progression, defined according to the IMWG 2016 response criteria for Multiple Myeloma<sup>21 26-28</sup>. This will include assessment of prognostic markers, markers of disease activity and M-protein levels. Analyses will include serum levels of beta-2 microglobulin, immunoglobulins IgG, IgA and IgM, kappa and lambda free immunoglobulin light chains. Serum electrophoresis and immunofixation, M-protein quantitation including total protein and densitometry. Urine immunofixation and free light chain quantitation will be performed where appropriate. As the trial proceeds new biomarkers of myeloma disease activity are likely to become available and will also be measured. The Laboratory will ensure that the Materials are received, handled, analysed, stored and destroyed in line with the individual consent provided.

### HMDS

The presence of minimal residual disease will be assessed in bone marrow aspirates using a validated flow cytometry assay (sensitivity  $\leq 0.001\%$ ) performed at a single central laboratory (HMDS, Leeds Teaching Hospitals Trust). A minimum of 2,500,000 cells will be evaluated with an eight-colour antibody combination of CD138, CD38, CD45, CD19, CD56, CD27, CD81 and CD117. Additional antigens for detection of CD38-negative plasma cells will be utilised as required. % neoplastic plasma cells and % normal plasma cells as a percentage of leucocytes will be reported. Limit of detection (LoD) and limit of quantification (LoQ) will also be calculated for each sample. Samples will be used for trial purposes only and will not be stored for future research.

## UCL

### **Bone marrow aspirates, peripheral blood and bone marrow trephine processing within UCL Myeloma Lab for RADAR clinical trial**

#### OBJECTIVES

To provide molecular and genetic data on bone marrow immune profiles of newly diagnosed myeloma patients prior and post autologous stem cell transplantation. This will also be analysed between study arms to compare how different treatment regimes alert immune landscape in patients in particular anti-CD38 mAb Isatuximab.

#### METHODS

##### BMA and PB:

1. Sites are requested to collect samples and ship as per Lab Manual together with completed sample request form.
2. All samples will be processed in Myeloma Lab at UCL Cancer Institute.
3. UCL ECMC GCLP Facility will serve as storage facility for the following materials: PB plasma, BM serum, pellets (BM, PB, CD138+ and CD138-), protein lysates, extracted RNA and DNA. All material to be stored at -80°C.
4. Myeloma Lab will serve as processing facility for all samples and storing of the following materials: BM MNCs (mononuclear cells), PB MNCs, CD138+ cells and CD138- cells. All material to be stored in liquid nitrogen.
5. Both -80°C freezers and liquid nitrogen tanks are temperature monitored with systems that alert when temperature is out of acceptable range.
6. All samples and material extracted will be logged into the trial specific lab book and database with a unique trial ID, lab ID and time-point.
7. Upon arrival bone marrow aspirates and peripheral blood will be centrifuged. Serum (from BMA) and plasma (from PB) will be collected, aliquoted into 1-1.5ml aliquots and frozen at -80°C.
8. BMA and PB mononuclear cells will then be isolated and enriched using Ficoll density gradient centrifugation.
9. PB MNCs will then be frozen as pellets and/or cryopreserved.
10. Depending on the tumour burden in the BM MNCs samples will be either frozen as MNCs pellets and/or cryopreserved or tumour cells will be isolated.

- 1
- 2
- 3 11. Tumour will be isolated via column-based MACS cell positive selection using CD138 magnetic
- 4 beads (MicroBeads).
- 5
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- 7 12. Depending on the number of cells isolated, CD138+ plasma cells will be frozen and stored as
- 8 pellets and/or protein lysates and/or cryopreserved.
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- 11 13. CD138- cells will be frozen and stored as pellets and/or cryopreserved.
- 12

#### Bone marrow trephine:

- 13
- 14
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- 16 1. Sites are requested to collect, process and ship samples as per Lab Manual together with
- 17 completed sample request form.
- 18
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- 20 2. Myeloma lab will serve as storage facility for bone marrow trephine slides.
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- 23 3. Upon arrival all samples will be logged into trial specific database with a unique trial ID, lab
- 24 ID and time-point.
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- 26 4. Upon arrival slides will be labelled and stored in the air-tight slide storage box.
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#### ANALYSIS

- 31
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- 34 1. High-dimensional flow cytometry will be used to profile immune context of patient bone
- 35 marrow mononuclear cells prior and post-transplant.
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- 37 2. Selected samples will be analysed further using transcriptomic profiling, T cell receptor (TCR)
- 38 sequencing or single cell sequencing and multiplex
- 39 immunofluorescence/immunohistochemistry on bone marrow trephine biopsies.
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# BMJ Open

## Risk and response adapted therapy following autologous stem cell transplant in patients with newly diagnosed multiple myeloma (RADAR (UK-MRA Myeloma XV Trial): study protocol for a Phase II/III randomised controlled trial

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	Asher, Samir; UCL Cancer Institute Yong, Kwee; UCL Cancer Institute
<b>Primary Subject Heading</b> :	Oncology
<b>Secondary Subject Heading</b> :	Haematology (incl blood transfusion)
<b>Keywords</b> :	Myeloma < ONCOLOGY, Myeloma < HAEMATOLOGY, Clinical trials < THERAPEUTICS, Cancer genetics < GENETICS, STATISTICS & RESEARCH METHODS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT



# Risk and response adapted therapy following autologous stem cell transplant in patients with newly diagnosed multiple myeloma (RADAR (UK-MRA Myeloma XV Trial): study protocol for a Phase II/III randomised controlled trial

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Word count: 8343

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## **Abstract**

### **Introduction**

Multiple myeloma is a plasma cell malignancy that accounts for 1-2% of newly diagnosed cancers. At diagnosis, approximately 20% of patients can be identified, using cytogenetics, to have inferior survival (high-risk). Additionally, standard-risk patients, with detectable disease (minimal residual disease (MRD)-positive) post-autologous stem cell transplant (ASCT), fare worse compared to those who do not (MRD-negative). Research is required to determine whether a risk-adapted approach post-ASCT could further improve patient outcomes.

### **Methods**

RADAR is a UK, multi-centre, risk-adapted, response-guided, open-label, randomised controlled trial for transplant-eligible newly diagnosed multiple myeloma patients, using combinations of lenalidomide (R), cyclophosphamide (Cy), bortezomib (Bor), dexamethasone (D) and isatuximab (Isa).

Participants receive RCyBorD(x4) induction therapy, followed by high-dose melphalan and ASCT. Post-ASCT, there are three pathways.

1. A phase III discontinuation design to assess de-escalating therapy in standard-risk MRD-negative patients. Participants receive 12 cycles of Isa maintenance. Those who remain MRD-negative are randomised to either continue or stop treatment.
2. A phase II/III multi-arm multi-stage design to test treatment strategies for treatment escalation in standard-risk MRD-positive patients. Participants are randomised to either; R, RBorD(x4) +R, RIsa, or RBorIsaD(x4) + RIsa.
3. A phase II design to assess the activity of intensive treatment strategies in high-risk patients. Participants are randomised to RBorD(x4) +R or RBorIsaD(x4) + RIsa.

1400 participants will be registered to allow for 500, 450 and 172 participants in each pathway. Randomisations are equal and treatment is given until disease progression or intolerance.

### **Ethics and dissemination**

Ethical approval was granted by the London–Central Research Ethics Committee (20/LO/0238) and capacity and capability confirmed by the appropriate local research and development department for each participating centre prior to opening recruitment. Participant informed consent is required before trial registration and re-confirmed post-ASCT. Results will be disseminated by conference presentations and peer-reviewed publications.

### **Trial registration**

ISCRTN 46841867

**Key Words: Newly Diagnosed, Multiple Myeloma, Transplant-eligible, Risk-adapted, Treatment escalation, Treatment de-escalation**

## **Article Summary**

### **Strengths and limitations of the study**

#### **Strengths**

- RADAR trial treatment is personalised through the utilisation of baseline cytogenetic and dynamic MRD-based stratification within its design
- RADAR is adaptive, new experimental treatment arms are expected to be added as new evidence emerges.
- RADAR has the potential to address an unmet need in post-ASCT treatment of multiple myeloma patients.
- RADAR includes the evaluation of a de-escalation strategy which will determine whether patients responding to treatment need to continue treatment until progression.

#### **Limitations**

- Patients achieving <PR to induction therapy will not proceed with on-study ASCT and will be treated off-trial, there is no trial pathway for these participants.
- RADAR excludes patients with impaired renal impairment (defined as CrCl <30 ml/min)
- The definition of high-risk used in RADAR may not be aligned to other international definitions, which may limit generalisability of outcomes

## **Introduction**

### **Multiple Myeloma**

Multiple myeloma (MM) is the second most common haematological malignancy with over 5500 patients diagnosed in the UK each year.[1] Whilst there is no established cure, survival has extended markedly in the last 15 years such that patients diagnosed today can expect to live a median of 6 years, and 30% will live for 10 years or longer.[1, 2]

These advances have been made possible due to the now standard use of “novel agents” including proteasome inhibitors and immunomodulatory agents (IMiD® agents) in conjunction with high-dose melphalan (HDM) supported by autologous stem cell transplantation (ASCT). Whilst MM is predominantly a disease of older people, around 40% of patients are young and fit enough at diagnosis to be eligible for ASCT, a strategy shown in several randomised trials (RCT) to extend progression-free survival (PFS).[2-4]

Improved response rates and increased survival poses challenges for the evaluation of new regimens in a timely manner. Recent studies re-evaluating the role of ASCT in the era of novel agents have confirmed superior PFS in patients allocated to ASCT compared to those allocated to chemotherapy with deferred ASCT.[5] No overall survival (OS) benefit has been seen yet, although this probably reflects the frequent use of salvage ASCT at second remission in most trial patients. Such studies utilise post-ASCT continuous therapy (lenalidomide maintenance) [6] that can extend PFS and OS,[7] but may also impact on quality of life (partly due to treatment-related toxicity), and are not without long-term risk.[8] It is thus imperative to identify those patients who are likely to benefit from extended maintenance therapy, in order to reduce health care costs and minimise toxicity for those who do not benefit.

### **Existing Evidence: Induction Therapy**

Treatment with lenalidomide (R), cyclophosphamide (Cy), bortezomib (Bor) and dexamethasone (D) (RCyBorD) was studied as first line therapy in the Phase 2 EVOLUTION study, where it produced high response rates and deep responses compared to CyBorD or LenBorD.[9]

### **Existing Evidence: High-Risk Patients**

At diagnosis, a small subgroup of patients (approximately 20%) can be identified on the basis of genetic features to have inferior survival regardless of treatment regimen (high-risk patients).[10-12] For such patients, and for those patients with refractory disease (no response to first line therapy), outcomes have remained poor despite the introduction of novel agents[13-15]. Whilst high-risk patients often show a good response to induction therapy, the durability of the response is inferior to standard-risk patients. Using the R-ISS which incorporates high risk cytogenetic features into the the International Staging System (ISS), PFS time is 66 months for R-ISS stage I, 42 months for R-ISS stage II, and 29 months for R-ISS stage III)[16]. The attainment of MRD-negative disease is also critical.[17-19] The activity of the RBorD regimen in patients with high-risk disease looks promising[20], and there is a question of whether an additional benefit may be gained through the use of anti-CD38 immunotherapy. Anti-CD38[21, 22] antibodies have single agent activity, but also impressive efficacy in combination, particularly with IMiD agents, lenalidomide and pomalidomide. In the RADAR trial the anti-CD38 antibody isatuximab (Isa) (SAR650984) will be used. Isatuximab is a naked immunoglobulin



(Ig) G1 derived monoclonal antibody (mAb) that binds selectively to a unique epitope on the human surface antigen called CD38 [23].

### **Existing Evidence: Standard-Risk Patients**

With increasingly effective multi-drug regimens being used for induction treatment, and responses further deepened following high-dose therapy and ASCT, the major challenge for standard-risk participants is how to maintain their disease control for as long as possible. The benefit of post-ASCT consolidation approaches remains controversial, with inconsistent evidence identifying both appropriate patient groups and treatment strategies.

Maintenance lenalidomide (R) has been studied within several large studies and has consistently been shown to increase PFS, confirmed within a recent meta-analysis.[7] The impact of long-term lenalidomide therapy on bone marrow and immune function, and general wellbeing are not completely understood. Thus there is an urgent need to identify those patients who benefit most from this approach, as well as an evaluation of other agents that utilise the host immune system to improve outcomes, such as antibodies. It is also of benefit to explore the option and effect of stopping maintenance therapy in patients who have achieved and maintained the deepest response

### **Existing Evidence: Use of MRD for stratifying treatment in standard-risk patients**

MRD status is a clinically relevant biomarker, and an emerging clinical trial endpoint with recent guidance published by the International Myeloma Working Group (IMWG).[19, 24]

Several studies have shown that patients who have detectable disease in their bone marrow (MRD-positive) following ASCT suffer earlier relapses and shorter survival when compared with those who are MRD-negative.[25, 26] These results have been combined in a recent meta-analysis.[26] Hence these patients should be the focus of investigative strategies aimed at deepening disease response and converting them from MRD-positive to MRD-negative.

Patients without detectable disease in their bone marrow (MRD-negative), have longer PFS and OS.[27] In the IFM2009 study that randomised patients to receive ASCT upfront or to continue chemotherapy, patients who were MRD-negative fared equally well, regardless of whether they had received ASCT, or chemotherapy alone. This would suggest that those who have achieved MRD-negative response may not need to undergo intensive consolidation therapy, and instead may benefit from a de-escalation of therapy.

### **Aims and objectives**

RADAR aims to address the most important contemporary therapeutic questions for newly diagnosed multiple myeloma transplant eligible (NDMM TE) patients post-ASCT by considering three different post-ASCT treatment pathways:

1. A de-escalation treatment strategy is used to determine whether ceasing Isa maintenance treatment, after 12 cycles of continuous treatment, is non-inferior to long-term Isa treatment, in terms of progression-free survival (PFS) in participants who are standard-risk at diagnosis (participants who have  $\leq 1$  high-risk cytogenetic lesion) and are MRD-negative at 100 days post-ASCT and 12 months (cycles) after.

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2. A treatment escalation strategy is used for participants who are standard-risk at diagnosis (participants who have  $\leq 1$  high-risk cytogenetic lesion) and MRD-positive at 100 days post ASCT. The trial aims to compare the activity and efficacy of post-ASCT consolidation and maintenance treatment between combinations of R, Bor, D and Isa to R alone in terms of conversion to MRD-negativity.
3. Dose-intensive consolidation and maintenance strategies will be studied for participants who are high-risk at diagnosis (participants who have  $> 1$  high-risk cytogenetic lesion). The activity of post-ASCT strategies containing R, Bor, D and Isa will be assessed in terms of PFS rate.

## Trial Design

RADAR is a national, multi-centre, risk-adapted, response-guided open-label, randomised controlled trial for NDMM TE patients: phase II/III for standard-risk, MRD-Positive participants, phase III randomised discontinuation design for standard-risk, MRD-Negative participants, phase II randomised for high-risk participants. The following report details the trial protocol and follows the structure of the SPIRIT statement.[28] The SPIRIT checklist can be found within the supplementary material.

## Methods:

### Setting

The RADAR trial will be conducted at 70 centres in the United Kingdom (See supplementary material), as identified via a feasibility assessment to determine those most appropriate to participate in the trial.

Potential participants will be identified by the research team at the time they are referred to the haematology outpatient department with suspected multiple myeloma. A smaller number of participants may be identified during inpatient admissions. Invitation to participate in the trial and provision of information will be made either during their first consultation, when routine diagnostic tests will be performed and potential treatment options discussed, or at the time they receive their diagnostic test results.

### Eligibility criteria

Adults (18 years and older) with previously untreated multiple myeloma requiring therapy, as defined by IMWG diagnostic criteria, who are eligible for stem cell transplant and capable of giving informed consent will be assessed for eligibility. Eligibility will be confirmed prior to; registration, the start of isatuximab maintenance treatment in the Randomisation 1 pathway and each randomisation by the principal investigator (PI) or an appropriately authorised medically trained delegate and will be recorded in the participants' medical records and on the relevant electronic case report form (eCRF).

To be eligible for each point in the trial the participants must meet all the inclusion criteria and none of the exclusion criteria presented in Table 1 for trial registration, Table 2 for isatuximab treatment in the R1 pathway, Table 3 for Randomisation 1 (R1), Table 4 for Randomisation 2 (R2), Table 5 for Randomisation 3 (R3).

Table 1: Inclusion and Exclusion Criteria for Main Trial Registration

<b>Inclusion Criteria:</b>	
1.	Previously untreated patients with multiple myeloma requiring therapy, defined as having myeloma defining events or with biomarkers of malignancy according to IMWG diagnostic criteria
2.	Eligible for stem cell transplant
3.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression);
4.	Total bilirubin $\leq 1.5$ x upper limit of normal (ULN)
5.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3$ x ULN (if ALT <b>and</b> AST are tested, both must meet this criteria)
6.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/L</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/L</math> is allowed),</li> <li>• haemoglobin (Hb) <math>\geq 80g/L</math>. Blood transfusions within 3 days prior to eligibility assessments are <b>not permitted</b>,</li> <li>• platelets <math>\geq 75 \times 10^9/L</math> (in the case of heavy bone marrow infiltration (&gt;50%) which is, in the opinion of the investigator, the cause of the thrombocytopenia and provided appropriate supportive measures and patient monitoring are in place, a platelet count of <math>\geq 50 \times 10^9/L</math> is permitted. Platelet transfusions within 3 days prior to eligibility assessments are <b>not permitted</b>.</li> </ul>
7.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
8.	Able to swallow oral medication
9.	Aged at least 18 years
10.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ol style="list-style-type: none"> <li>a) Are not of childbearing potential (Appendix 7), OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest, OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ol style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Contraception for female and male participants must be in accordance with (and participants must consent to) the Celgene Pregnancy Prevention Plan.</p> <p>If female and of childbearing potential, they must have a negative pregnancy test performed by a healthcare professional within 14 days prior to registration.</p>
11.	Able to provide written informed consent.
<b>Exclusion Criteria</b>	
1.	Asymptomatic (smouldering) MM, monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma of bone, or extramedullary plasmacytoma (without evidence of MM)

2. Received previous treatment for MM, with the exception of local radiotherapy to relieve bone pain or spinal cord compression, prior bisphosphonate treatment, or corticosteroids as long as the total dose does not exceed the equivalent of 160mg dexamethasone. *This criteria is not applicable at R1, R2 and R3 when participants will have received previous treatment for MM as part of this trial.*
3. Unstable angina or myocardial infarction within 4 months prior to registration (or at any time since registration for participants starting isatuximab maintenance, R1, R2 and R3), NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
4. Cardiac disorder identified according to local practice (eg left ventricular ejection fraction, LVEF; results from formal measurements acceptable within 28 days prior to registration)
5. Significant neuropathy (Grade  $\geq 3$ , or Grade 2 with pain)
6. Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to registration. Cancer treated with curative intent for >5 years previously and without evidence of recurrence will be allowed.
7. Pregnant, lactating or breastfeeding female participants
8. Known resistance, intolerance or hypersensitivity to any component of the planned therapies, except in the case of hypersensitivity which is amenable to premedication with steroids or H2 blocker. Intolerance includes hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
9. Major surgery within 14 days before registration (or starting isatuximab maintenance, R1, R2 and R3). This would include surgical intervention for relief of cord compression but does not include vertebroplasty or kyphoplasty.
10. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of trial treatment, including difficulty swallowing.
11. Active systemic infection
12. Participant is hepatitis B surface antigen positive, hepatitis C antibody positive or HIV positive (participants who are hepatitis C core antibody positive but have been successfully treated for the disease may still be eligible – please consult the CTRU/CI). Participants must have hepatitis and HIV screening conducted within 28 days prior to registration.
13. Any other medical or psychiatric condition which, in the opinion of the investigator, contraindicates the participant's participation in this study.
14. Receipt of live vaccination within 30 days prior to registration, for the duration of the study and for 3 months after the last dose of study drug.
15. Participant has risk factors for thromboembolism including the use of agents which may increase their risk of thrombosis, such as hormone replacement therapy (*this exclusion criteria is applicable only at registration and when starting R2 or R3 pathway*)
16. Participant has risk factors for seizures (*this exclusion criteria is applicable only at registration and when starting R2 or R3 pathway*)

Table 2: Inclusion and Exclusion criteria for Isatuximab treatment (R1 Pathway)

<b>Inclusion Criteria:</b>	
<ol style="list-style-type: none"> <li>1. Standard-risk (participant is not <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q), as confirmed by the CTRU.</li> <li>2. 4 cycles of RCyBorD received</li> <li>3. MRD-negative (proportion of malignant cells in the bone marrow is &lt; 1 in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT</li> <li>4. Received <math>\geq 100\text{mg/m}^2</math> high-dose melphalan and ASCT</li> <li>5. Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG &gt;2 is due to effects of myeloma eg spinal cord compression)</li> <li>6. Total bilirubin <math>\leq 1.5 \times</math> upper limit of normal (ULN )</li> <li>7. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) <math>\leq 3 \times</math> ULN (if ALT <b>and</b> AST are tested, both must meet this criteria)</li> <li>8. Adequate marrow function:               <ol style="list-style-type: none"> <li>a) neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>b) Hb <math>\geq 80\text{g/L}</math>. Blood transfusions within 3 days prior to eligibility assessments are not permitted,</li> <li>c) platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> </ol> </li> <li>9. Creatinine clearance (CrCl) <math>\geq 30</math> mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)</li> <li>10. Agree to follow the pregnancy prevention guidelines:               <p>Female participants who:</p> <ol style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ol style="list-style-type: none"> <li>e) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest OR</li> <li>f) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest.. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>g) Agree to not donate sperm during the entire study treatment period until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> </li> <li>11. Signed the Informed Consent Document for the R1 treatment pathway.               <ol style="list-style-type: none"> <li>a)</li> </ol> </li> </ol>	
<b>Exclusion Criteria:</b>	
<ol style="list-style-type: none"> <li>1. Disease progression (according to IMWG criteria)</li> <li>2. MRD-positive (proportion of malignant cells in the bone marrow is <math>\geq 1</math> in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT</li> <li>3. Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)</li> </ol>	

Table 3: Inclusion and Exclusion criteria for Randomisation 1

<b>Inclusion Criteria:</b>	
1.	Standard-risk (participant is not <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q), as confirmed by the CTRU.
2.	12 cycles of isatuximab maintenance received
3.	MRD-negative (proportion of malignant cells in the bone marrow is < 1 in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT
4.	MRD-negative (proportion of malignant cells in the bone marrow is < 1 in 100,000, confirmed by HMDS central lab) after 12 cycles of isatuximab
5.	Received $\geq 100\text{mg/m}^2$ high-dose melphalan and ASCT
6.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression)
7.	Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN )
8.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3 \times$ ULN (if ALT and AST are tested, both must meet this criteria)
9.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>• Hb <math>\geq 80\text{g/L}</math>. Blood transfusions within 3 days prior to eligibility assessments are not permitted,</li> <li>• platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> </ul>
10.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
11.	Agree to follow the pregnancy prevention guidelines: <p style="margin-left: 20px;">Female participants who:</p> <ul style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 5 months after the last dose of study drug, OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject from the time of signing the informed consent form until 5 months after the last dose of study drug. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 5 months after the last dose of study drug.</li> </ul> <p style="margin-left: 20px;">Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ul style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 5 months after the last dose of study drug, OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 5 months after the last dose of study drug. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until 5 months after the last dose of study drug.</li> </ul>
12.	Signed the Informed Consent Document for the R1 treatment pathway.
<b>Exclusion Criteria</b>	
1.	Disease progression (according to IMWG criteria)
2.	MRD-positive (proportion of malignant cells in the bone marrow is $\geq 1$ in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT or after 12 cycles of isatuximab
3.	Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)

Table 4: Inclusion and Exclusion Criteria for Randomisation 2

<b>Inclusion Criteria:</b>	
1.	Standard-risk (participant is not <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q) as confirmed by CTRU.
2.	4 cycles of RCyBorD received
3.	MRD-positive (proportion of malignant cells in the bone marrow is $\geq 1$ in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT
4.	Received $\geq 100\text{mg}/\text{m}^2$ high-dose melphalan and ASCT
5.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression)
6.	Total bilirubin $\leq 1.5$ x upper limit of normal (ULN )
7.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3$ x ULN (if ALT and AST are tested, both must meet this criteria)
8.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>• Hb <math>\geq 80\text{g}/\text{L}</math></li> <li>• platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> </ul>
9.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
10.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ul style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ul style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul>
11.	Signed the Informed Consent Document for the R2 treatment pathway.
<b>Exclusion Criteria:</b>	
1.	Disease progression (according to IMWG criteria)
2.	Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)

Table 5: Inclusion and Exclusion criteria for Randomisation 3

<b>Inclusion Criteria:</b>	
1.	High-risk (participant is <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q)) as confirmed by CTRU.
2.	4 cycles of RCyBord received
3.	Received $\geq 100\text{mg}/\text{m}^2$ high-dose melphalan and ASCT
4.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression)
5.	Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN )
6.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3 \times$ ULN (if ALT and AST are tested, both must meet this criteria)
7.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>• Hb <math>\geq 80\text{g}/\text{L}</math></li> <li>• platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> <li>• Creatinine clearance (CrCl) <math>\geq 30 \text{ mL}/\text{minute}</math>, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)</li> </ul>
8.	Creatinine clearance (CrCl) $\geq 30 \text{ mL}/\text{minute}$ , according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
9.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ol style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ol style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol>
10.	Signed the Informed Consent Document for the R3 treatment pathway.
<b>Exclusion Criteria</b>	
1.	Disease progression (according to IMWG criteria)
2.	Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)



## Interventions and Dosing

### *Intervention Schedule*

All participants will receive four, 21 day, cycles of induction treatment with RCyBorD. During this time, the genetics risk status of the participant will be analysed and determined from bone marrow samples prior induction treatment (from diagnosis or trial-specific procedures). Participants will either be allocated as high risk (defined as the presence of at least 2 of these adverse lesions: t(4,14), t(14,16), t(14,20), del(17p) or gain(1q)) or standard risk. At the end of the induction cycle participants will be assessed for response. In the absence of disease progression or intolerance, participants with at least a partial response (PR) will proceed to HDM and ASCT which will be carried out according to local practice. At 100 days post-ASCT participants will be assessed for MRD and response and will follow one of three pathways of post ASCT treatment, provided they meet the eligibility criteria:

1. Participants identified as standard risk and who are MRD-negative post-ASCT will be treated according to the R1 pathway. All participants will receive 12 cycles of Isa maintenance treatment. Those who remain MRD-negative following cycle 12, will be randomised to continue or stop Isa maintenance treatment.
2. Participants identified as standard-risk and who are MRD-positive post-ASCT and have at least a minimal response (MR) at 100 days post ASCT, will proceed to R2. Eligible participants will be randomised between: R maintenance; RBorD consolidation and R maintenance (RBorD + R); RIsa maintenance; or RBorIsaD consolidation and RIsa maintenance (RBorIsaD + RIsa).
3. Participants identified as high-risk and have at least a partial response (PR) at 100 days post ASCT will proceed to R3. These participants will be randomised to receive either RBorD consolidation, followed by R maintenance; or RBorIsaD consolidation followed by RIsa maintenance.

All randomisations are balanced across the treatment arms. A computer generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well balanced for the stratification factors of each randomisation (See Table 6).

Table 6: Stratification Factors

Randomisation:	Stratification factors:
1	<ul style="list-style-type: none"> <li>• Centre</li> <li>• Number of high risk lesions at trial registration (0 or 1 or unable to determine)</li> </ul>
2	<ul style="list-style-type: none"> <li>• Centre</li> <li>• Number of high risk lesions at trial registration (0 or 1 or unable to determine)</li> <li>• Response at 100 days post-ASCT (<math>&lt; VGPR</math>, <math>\geq VGPR</math>)</li> </ul>
3	<ul style="list-style-type: none"> <li>• Centre</li> <li>• Number of high risk lesions at trial registration (2, or <math>\geq 3</math>, or unable to determine)</li> <li>• Response at 100 days post-ASCT (<math>&lt; VGPR</math>, <math>\geq VGPR</math>)</li> </ul>

Table 7 summarises the starting doses for the induction treatment and each post-ASCT treatment pathway. Following ASCT all treatments will continue until disease progression or intolerance. Response will be assessed at the end of each cycle according to the IMWG 2016 response criteria[24, 29-31]. Treatment intolerance will be assessed throughout each treatment cycle, according to the national cancer institute (NCI) common terminology criteria for AE (CTCAE) Version 5. All consolidation cycles are 21 days in length, maintenance cycles are 28 days in length.

Table 7: Dosing schedule for R<sub>Cy</sub>BorD induction and each randomisation pathways

<b>Trial Registration- Induction (Each cycle = 21 days)</b>		
<b>Treatment (Route)</b>	<b>Induction – All participants (Starting Dose)</b>	<b>Days</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup>	1, 8, 15
<b>Cyclophosphamide (PO)</b>	500mg	1, 8
<b>Lenalidomide (PO)</b>	25mg	1-14
<b>Dexamethasone (PO)</b>	40mg	1, 8, 15
<b>Isatuximab Pre-Randomisation 1 (Each cycle = 28 day)</b>		
<b>Treatment (Route)</b>	<b>R1 pathway participants Only (Starting Dose)</b>	<b>Days</b>
<b>Isatuximab (IV)</b>	10mg/kg	1, 8, 15 and 22 cycle 1 then days 1 and 15 from cycle 2 onwards
<b>Randomisation 1: Isatuximab maintenance (Each Cycle = 28 days)</b>		
<b>Treatment</b>	<b>Isatuximab (Days)</b>	<b>“Stop Isatuximab” (Days)</b>
<b>Isatuximab (IV)</b>	10mg/kg (Day 1 Only)	None
<b>Randomisation 2: MRD-positive treatment escalation pathway</b>		
<b>Treatment Arm 1 (Control) : Lenalidomide (R) maintenance</b>		
<b>Treatment (Route)</b>	<b>Starting Dose (Days)</b>	
<b>Lenalidomide (PO)</b>	10mg/kg* (1-21 )	
<b>Treatment Arm 2: R<sub>BorD</sub> consolidation + R Maintenance</b>		
<b>Treatment</b>	<b>Consolidation: Cycle 1-4 (each cycle = 21 days)</b>	<b>Maintenance (each Cycle = 28 days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)
<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA
<b>Treatment Arm 3:R<sub>Isa</sub> Maintenance</b>		
<b>Treatment</b>	<b>Maintenance (Days)</b>	
<b>Lenalidomide (PO)</b>	10mg* (Day 1-21)	
<b>Isatuximab (IV)</b>	10mg/kg (1, 8, 15 and 22 cycle 1 then days 1 and 15 from cycle 2 onwards)	
<b>Treatment Arm 4: R<sub>BorIsaD</sub> + R<sub>Isa</sub></b>		
<b>Treatment</b>	<b>Consolidation Cycle 1-4: Each cycle = 21 days (Days)</b>	<b>Maintenance: Each cycle = 28 days (Days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)
<b>Isatuximab (IV)</b>	10mg/kg (1, 8, 15 cycle 1 then days 1 and 8 cycle 2, then days 1 and 15 cycle 3 onwards)	10mg/kg (1 and 15)
<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA
<b>Randomisation 3: High Risk Treatment Pathway</b>		
<b>Treatment Arm 1: R<sub>BorD</sub> Consolidation and R maintenance</b>		
<b>Treatment</b>	<b>Consolidation: Cycle 1-4 (each cycle = 21 days)</b>	<b>Maintenance (each Cycle = 28 days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)

<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA
<b>Treatment Arm 2: RBorIsaD consolidation + RIsa Maintenance</b>		
<b>Treatment</b>	<b>Consolidation Cycle 1-4: Each cycle = 21 days (Days)</b>	<b>Maintenance: Each cycle = 28 days (Days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)
<b>Isatuximab (IV)</b>	10mg/kg (1, 8, 15 cycle 1 then days 1 and 8 cycle 2, then days 1 and 15 cycle 3 onwards)	10mg/kg (1 and 15)
<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA

\*or final dose administrated at the end of induction or consolidation treatment if lower

### *Intervention Adherence*

Throughout the trial R will be taken orally and swallowed whole at the same time on the scheduled days. D and Cy will be taken orally, whilst Bor will be administrated via a subcutaneous injection. Bortezomib may also be administered at home if this is in line with local policies and if appropriate procedures are in place. Isa will be given as an intravenous infusion and at a facility capable of managing hypersensitivity reactions.

To monitor adherence to the oral trial medicines, participants will complete a participant diary card which will be reviewed at each trial visit. Non-compliance will be reported to the CTRU and any unused capsules will be returned to the pharmacy.

### *Dose Modifications and Discontinuations*

With the exception of Isa, which can only be interrupted and resumed, dose modifications are permitted in the management of toxicities. Upfront dose modifications in response to liver and/or renal impairment are also permitted within the protocol. When the dose of any drug is reduced the dose cannot be re-escalated in this trial.

If one drug in a combination is stopped, treatment with the other drugs in combination can continue. Scenarios in which the participant may remain on trial following consultation with the Chief Investigator (CI) are if they: discontinue two or more drugs during combination therapy; cease treatment for more than three weeks in between any treatment cycle or are delayed in starting maintenance of consolidation beyond 120 days post-ASCT. Note that if Bor, R or D is stopped during the pre-ASCT induction treatment due to toxicity, the participant will only be able to be treated on the standard-risk-MRD-negative pathway (assuming they meet the relevant inclusion criteria).

If treatment is discontinued early, the participant will be treated off trial at the discretion of their treating clinician.

### *Concomitant medication:*

Local support care protocols, including anti-emetic schedules, tumour lysis syndrome prevention, venous thromboembolism prophylaxis and prophylactic antimicrobial therapy should be followed. The excluded concomitant medications and procedures whilst receiving trial treatment are listed in supplementary material.

1  
2  
3 Concomitant medication, disease and other malignancies will be recorded at eligibility.  
4  
5

## 6 **Outcomes:**

### 7 *Primary outcomes*

8  
9 PFS-R1 is defined as the time from R1 to the time of first documented evidence of disease progression  
10 or death from any cause. Individuals who are lost to follow-up or progression-free at the time of  
11 analysis will be censored at their last known date to be alive and progression-free.  
12  
13

14 Attainment of MRD-negativity is defined as a binary endpoint. MRD-negativity will be determined at  
15 6 months post-R2 (end of cycle 6 post-ASCT treatment for participants allocated to maintenance only  
16 strategies and end of cycle 7 post-ASCT treatment for participants allocated to maintenance and  
17 consolidation strategies) according to the IMWG 2016 response criteria.  
18  
19

20 The PFS rate is defined as the proportion of participants who are alive and progression-free 28 months  
21 post-R3.  
22  
23

24 Disease progression is defined according to the IMWG 2016 response criteria for Multiple Myeloma  
25 [24, 29-31].  
26

### 27 *Secondary outcomes:*

28 The secondary outcomes of this trial are to assess; PFS for R2 and R3, Time to progression, Time to  
29 second PFS event (PFS2), Overall survival (OS), Survival after progression, Objective response rate  
30 (ORR), Attainment of Very Good Partial Response ( $\geq$  VGPR), Attainment of MRD negativity, Duration  
31 of MRD Negativity, Time to improved response, Time to next treatment, Treatment compliance and  
32 total amount of therapy delivered, Toxicity and Safety, including the incidence of second malignancies,  
33 Quality of life (QoL) including EORTC-QLQ-C30, EORTC-QLQ-MY20 and EQ-5D-3L and Cost  
34 effectiveness.  
35  
36  
37  
38

### 39 *Exploratory and subgroup analyses*

40 An overview of the planned exploratory and subgroup analysis can be found in the supplementary  
41 material. These include genetic and molecular analysis of participant samples conducted by the  
42 respective central laboratories, as well as additional analysis to review the infection and re-infection  
43 rates of covid-19 in participants during induction, post-ASCT and during post ASCT consolidation.  
44  
45  
46

## 47 **Participant's timelines**

48 The full trial schema can be seen in Figure 1. The schedule of assessments at each time point are  
49 presented in Figure 2.  
50  
51

### 52 *Trial Entry*

53 Participants will enter into the trial at one of two points in their pathway, this will either be at bone  
54 marrow registration or at main trial registration.  
55  
56  
57  
58  
59  
60

### *Trial Consent*

Participants who enter the trial at bone marrow registration will provide consent to have bone marrow samples taken and sent to central laboratories for analysis. If the participant does not have myeloma or decides to not take part in RADAR, they will have the option of consenting to their samples being used in future research.

All participants will be required to provide written informed consent for the trial prior to trial registration (for initial trial treatment and further trial information) and prior to starting their post-ASCT treatment pathway once their post-ASCT assessments have been completed (for their pathway specific treatment). Optional consent regarding QoL and healthcare resource use questionnaires and the use of samples for future research will also be obtained within the first consent process.

Consent forms are included in supplementary material.

### *Trial Registration*

Following initial consent, participant eligibility for trial registration will be assessed. Trial samples for blood and urine will be taken for all participants and bone marrow samples will be taken for those who did not enter the trial through bone marrow registration.

### **Genetic Risk**

Bone marrow samples from diagnosis will be analysed at time of diagnosis at local cytogenetics laboratories for FISH-defined high-risk makers. Original/copy of the FISH testing report will also be sent to CTRU where they will be reviewed by the CI/Trial management team for risk stratification. Participants will either be categorised high-risk (defined as the presence of at least 2 of the following adverse lesions: t(4;14), t(4;16), t(14;20), del(17p) or gain(1q)) or standard-risk.

Participants will commence RCyBorD treatment once a diagnosis of symptomatic myeloma has been confirmed by the treating physician, and ideally when it is known that the FISH testing has been successful.

Where risk status can be determined from the first sample participants can continue on the trial. If status cannot be confirmed and the FISH report shows a full test failure i.e. no information relating to adverse lesions is available, a second attempt will be made to collect a bone marrow sample prior to treatment starting. If partial results are obtained from the FISH sample, it may be possible that the CI/trial management group (TMG) will be able to determine risk status using the assumption that translocations are mutually exclusive and that some markers are rare. If risk status can be determined a second bone marrow sample is not required. However, this must be confirmed by the CTRU.

If, after two bone marrow samples, the FISH results for some or all the adverse lesions are inconclusive participants risk will be determined using a combination of the results from the two samples. The most appropriate pathway will be determined by the CI. Note this may result in the participants stratification factor being 'unable to determine' at randomisation. If a second bone marrow has been requested by CTRU but the collection was not attempted, the participants will be taken off the study (after ASCT, if induction treatment was already started)

### *Induction and ASCT*

Following trial registration, once all central samples have been taken and risk status confirmed, participants will receive induction treatment as described in the intervention section. In the absence of disease progression or treatment intolerance participants with at least a partial response (PR) to will proceed to HDM and ASCT.

Consenting participants will complete QoL and resource use questionnaires at the end of RCyBorD induction treatment.

All participants who go through ASCT will have a bone marrow sample taken at 100 days (+/- 14) post-ASCT. If an MRD result cannot be obtained at the first attempt, the bone marrow will be repeated once (within 28 days after 100 days post-ASCT time point). If the second attempt fails, the participant will be considered MRD-positive.

### *Post-ASCT Treatment*

Participants who receive all 4 cycles of induction treatment followed by ASCT will be assessed for eligibility into their assigned randomisation pathways determined by genetic risk and MRD results and treated as described in the intervention schedule.

Consenting participants in the R1 pathway will complete QoL and resource use questionnaires after cycle 6, 12, 24 and 36 (participants randomised to "stop Isa" will complete the cycle 24 and 36 QoL and resource use questionnaires at equivalent time points).

Similarly, consenting participants to receive R or RI<sub>sa</sub> within pathway R2 and R3 will complete QoL and resource use questionnaires after cycles 6, 12 and 24 of maintenance. Those randomised to receive RBorI<sub>sa</sub>+R or RBorI<sub>sa</sub>D+RI<sub>sa</sub> will complete QoL and resource use questionnaires after cycles 3, 9 and 21 of maintenance.

Post-ASCT treatment (including observation only in the R1 pathway) is continued until disease progression, participant or clinician withdrawal or death. After treatment discontinuation, the participant is treated off trial by their local clinician and followed-up as per the trial follow-up schedule.

### *Trial Follow-up*

Participants who discontinue during induction and until 100 days post-ASCT will be followed up for data pertaining to safety, details of salvage treatment, progression (including second progression), and survival at standard care visits. Follow ups will be conducted every 2 months up until disease progression, death or the end of trial. Similar follow-up will be completed for participants who discontinue their allocated trial treatment, which started post-ASCT. In addition consenting participants will still complete QoL and resource use questionnaires at appropriate time points.

All types of adverse event/reaction will be collected until 60 days after the last dose of protocol treatment.

1  
2  
3 Following disease progression all participants will be followed up annually until death, or until the end  
4 of the trial.  
5  
6

### 7 **Sample size**

8  
9 In total 1400 participants will be recruited into the trial. Accounting for participants who will be lost  
10 to follow-up, this allows for 500, 450 and 172 participants to enter each randomisation, respectively.  
11  
12

#### 13 *Randomisation 1*

14 Data from our previous trial Myeloma XI, suggests that approximately 50 participants will lose their  
15 MRD-negative status during the first 12 cycles of Isa maintenance. In addition, Myeloma XI estimated  
16 median PFS with continuous R to be 50 months amongst TE participants.[32] Under these assumptions  
17 and allowing for our randomisation being 12 months later, 500 participants allows for 80% power to  
18 test a non-inferiority margin of 10% at 2 years post-R1 (this equates to a hazard ratio of 1.38) with a  
19 one-sided 5% significance level, allowing for approximately 20% further drop-out after R1 amongst  
20 participants unwilling to cease treatment or being lost to follow-up.  
21  
22  
23

24  
25 A power of 80% will be attained when 238 PFS events have been observed. These calculations assume  
26 that PFS follow an exponential distribution and that there will be 3 years of recruitment to R1 and 2  
27 further years of follow-up (in order that all participants can have PFS at 2 years post-R1 assessed).  
28  
29

30 Global Health Status/Quality of Life is considered a key secondary endpoint of R1 as the conclusion  
31 that the cessation of continuous treatment is non-inferior should not come at the expense of quality  
32 of life. Ignoring those required to account for participants lost to follow-up, the 406 participants  
33 recruited above give >95% power to detect a difference of 10 points at 2 years post-R1, where 10  
34 points represents an accepted medium magnitude clinically relevant difference.[33] The calculation  
35 uses data collected from the intensive pathway of MRC Myeloma IX to estimate that the standard  
36 deviation in the Global Health Status/QoL subscale of EORTC-QLQ-C30 as 27.54 along with a two-sided  
37 5% significance level.[34]  
38  
39  
40  
41  
42

#### 43 *Randomisation 2*

44 R2 is a multi-arm, multi-stage drug/drug-combination assessment platform with seamless phase II  
45 (activity) and phase III (efficacy) stages. Each experimental arm is compared with a designated control  
46 arm (R maintenance).  
47  
48

49 Early data from Myeloma XI and similar data from IFM/DFCI 2009 [35] suggest that a 10% upgrade in  
50 MRD-negative rate after 6 months continuous R treatment is achievable. It is thought that RBoRD  
51 consolidation followed by attenuated continuous R or continuous R combined with antibody or  
52 immunotherapy could lead to a 30% increase in MRD-negative rate, a 20% upgrade of increase at 6  
53 months post-randomisation when compared to continuous R treatment, as good as therapy  
54 combinations containing an alternative proteasome inhibitor.<sup>33</sup>  
55  
56  
57

58 Following the strategy of Bratton and colleagues [36] for a multi-arm multi-stage trial with:

- 59 • N=2 stages (Stage 1 (activity) and Stage 2 (efficacy)) and  
60

- J=4 experimental arms (R<sub>BorD</sub>+R, R+I<sub>sa</sub>, R<sub>BorI<sub>sa</sub>D</sub> + I<sub>sa</sub> and TBC) and a single control arm (R)
- Where allocation is equal across each arms (1:1:1:1:1) and
- The power in Stage 1 and Stage 2 is 95% and 85%, respectively,
- the one-sided significance level in Stage 1 and Stage 2 is 25% and 1%, respectively,
- 10 participants per month are entered at R<sub>2</sub>, Stage 1 (activity) analysis and reporting requires 1 month and 5% of participants drop-out.

This equates to 40 participants in each arm at Stage 1 and 50 further participants in each arm at Stage 2. This will require a maximum of 46 months of recruitment plus a further 6 months of follow-up for the final participant. Overall, this design has a power of 83.4% and a one-sided family-wise error rate (FWER) of ~3%.

Randomisation 2 has been powered assuming four experimental arms and that all experimental arms will continue to stage 2. In the case that only three experimental arms are implemented or at least one experimental arm is concluded to show a lack of activity after stage 1, the trial will have a higher power than stated above.

### *Randomisation 3*

Each arm of R<sub>3</sub> will take the form of one-stage treatment design proposed by Simon, Wittes and Ellenberg [37] where the A'Hern design [38] is first implemented to determine treatment activity in both arms. Treatment activity will be determined by considering the PFS rate at 28 months. Data from Myeloma XI demonstrated a median PFS for high-risk participants in the intensive pathway of approximately 19 months (unpublished data). It is thought that for the treatments proposed to be investigated further in a Phase III trial they should increase the median PFS from 19 months to at least 28 months (9 month increase), i.e. increasing the PFS rate at 28 months from 34.7% to 50%.

In order to have an 80% power of demonstrating that the one-sided 95% confidence interval of the PFS rate at 28 months excludes 34.7%, 81 evaluable participants are required, where a treatment arm will be deemed a "success" if at least 37 out of 81 participants are progression-free at 28 months. To account for approximately 5% of participants being unevaluable at 28 months post-R<sub>3</sub>, 86 participants will be randomised to each treatment arm i.e. 172 participants are required to be entered into R<sub>3</sub>.

### *Total Study Sample Size*

Accounting for those participants who will be lost-to-follow-up R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> require 500, 450, and 172 participants to enter each randomisation respectively.

Considering R<sub>1</sub> and R<sub>2</sub>, it is assumed that 50 participants will lose their MRD-negative status during the 12 months of continuous treatment (Myeloma XI, unpublished data). Therefore 550 participants are required to enter the MRD-negative part of the standard-risk pathway. It is assumed that 55% of standard-risk participants will be MRD-negative at the point of assessment therefore approximately 1000 participants are required to reach the MRD assessment stage of the standard-risk pathway [35, 39] It is assumed that 90% of all those recruited will reach this point therefore 1112 participants are required to enter the standard-risk pathway[5] . It is anticipated that 80% of all those recruited will be standard-risk (Myeloma XI, unpublished data) therefore at least 1390 participants are required to be recruited to the trial. Rounding this we obtain an overall sample size of 1400.



1  
2  
3  
4 This gives 280 participants who are expected to enter the high-risk pathway, using the same logic as  
5 in the standard-risk pathway if 90% of participants reach R3 then there will be approximately 252  
6 participants recruited to R3. Given the calculations above it is plausible that another arm could be  
7 added to the high-risk pathway at a later date.  
8  
9

#### 10 *Recruitment:*

11 It is planned that 1400 participants will be recruited for a total of 36 months. Once all centres are  
12 open, the recruitment target is 38 participants a month (equating to approximately 30 standard risk  
13 and 8 high-risk participants).  
14  
15  
16

17 In order to ensure the trial will meet the target sample size within the recruitment period, site set-up  
18 was prioritised whilst the trial was preparing to open to recruitment. In addition, the trial team are  
19 actively engaging with Principal Investigators at sites who support the trial to ensure that those sites  
20 open quickly and are maintaining regular communication with open sites to ensure that they continue  
21 to recruit to the trial.  
22  
23  
24

25 The trial opened to recruitment on 11/05/2021.  
26  
27

#### 28 **Assignment of treatment allocations:**

29 Each of the registration and randomisation procedures will be conducted centrally using the University  
30 of Leeds Clinical Trial Research Unit (CTRU) automated 24-hour web base and telephone system.  
31  
32

#### 33 **Registration**

34 If a patient is suspected to have myeloma they will enter the trial at the time of routine diagnostic  
35 tests, through bone marrow registration. Once diagnosis is confirmed locally and the research team  
36 consider the patient potentially eligible for the trial, patients will be provided with full verbal  
37 explanation of the trial and full participant information sheet and informed consent documents to  
38 consider. Once the patient has provided informed consent to the first stage of the trial they will be  
39 registered into the trial at Bone Marrow Registration.  
40  
41  
42  
43

44 Patients who have already had Myeloma confirmed prior to being approached for the trial, and those  
45 who decline consent at bone marrow registration, will enter at main trial registration.  
46  
47

#### 48 **Data Collection**

49 Data collection will primarily be via Remote Data Entry (RDE) on electronic case report forms (eCRFs),  
50 provided by the CTRU at the University of Leeds, and will be entered by staff at the research site.  
51 Access to the live RADAR database will be provided by the CTRU following sites being authorised to  
52 open to recruitment; guidance on RDE and completing eCRFs will be provided. Data regarding  
53 informed consent, QoL, Healthcare Resource Use questionnaires and in-patient stay forms will be  
54 collected via paper case report forms.  
55  
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1  
2  
3 QoL and Healthcare Resource Use questionnaires will be completed by the participant in clinic or at  
4 home and sealed in an envelope before handing back to the site research team who will return them  
5 to the CTRU via post.  
6  
7

### 8 **Data Management**

9  
10 All information collected during the course of the trial will be kept strictly confidential. Information  
11 will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of  
12 the Data Protection Act 2018.  
13  
14

15 Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it  
16 is received, confirmed as not available or the trial is at analysis. The CTRU/Sponsor will reserve the  
17 right to intermittently conduct source data verification exercises on a sample of participants, which  
18 will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access  
19 to participant notes at the participating hospital sites and the ongoing central collection of copies of  
20 Informed Consent Documents and other relevant investigation reports.  
21  
22

### 23 **Statistical methods**

24  
25 Statistical analysis is the responsibility of the CTRU statisticians, with the exception of the cost-  
26 effectiveness analysis, which will be undertaken by the health economists at the University of Leeds.  
27 A full statistical analysis plan (SAP) and Health Economics Analysis Plan (HEAP) will be written and  
28 approved before any analyses are undertaken.  
29  
30  
31

32 The analysis population will depend on the randomisation. Separate intention to treat (ITT), per  
33 protocol (PP) and safety populations will be defined for each randomisation. In either case the ITT  
34 population will include participants according to their randomisation allocation, regardless of  
35 eligibility whether they prematurely discontinued the treatment, or did not comply with the regimen.  
36 The PP population will exclude individuals who do not receive their randomisation allocation or who  
37 are found to be ineligible following randomisation. The safety population will consist of all participants  
38 who receive at least one dose of the trial treatments and analyse participants according to what they  
39 received rather than what they were randomised to.  
40  
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43  
44 With the exception of two interim analyses, no other formal analysis is planned until participants have  
45 attained the primary endpoint for each of the randomisations.  
46  
47

#### 48 *Primary endpoint analyses*

##### 49 Randomisation 1

50  
51 The primary endpoint for R1 will be attained 2 years after the final participant has been randomised  
52 to R1.  
53  
54

55 As R1 is a non-inferiority trial, both PP and ITT population analyses will be used as co-primary analyses  
56 and both are required to demonstrate statistical significance of non-inferiority where any  
57 discrepancies will be reported.  
58  
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2  
3 PFS at R1 will be assessed using Cox proportional hazards regression to adjust for the stratification  
4 factors of R1 excluding centre, and presented using Kaplan-Meier estimates of the survival function.  
5 The treatment cessation strategy will be declared non-inferior to the continuous treatment strategy  
6 if the upper bound of the one-sided 95% confidence interval for the hazard ratio is less than 1.38. Note  
7 no adjustment will be made for interim analysis due to it being a test for inferiority (see below) and  
8 not non-inferiority.  
9  
10

### 11 12 Randomisation 2

13 The primary endpoint for R2 will be attained 6 months after the final participant has been randomised  
14 to R2. Primary analysis will be undertaken on the ITT population.  
15  
16

17 An overall one-sided approximately 3% FWER will be applied accounting for each pair-wise  
18 comparison over each stage and all comparisons. This equates to a 25% and 1% one sided significance  
19 level at interim and final analysis. MRD-negative rate will be compared between each pair-wise  
20 comparison (experimental vs control) in turn using logistic regression and adjusted for the  
21 minimisation factors of R2 excluding centre.  
22  
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24

### 25 Randomisation 3

26 The primary endpoint for R3 will be attained 28 months after the final participant has been  
27 randomised to R3.  
28  
29

30 Primary analysis will be undertaken on the ITT population. The number of participants who are alive  
31 and progression-free at 28 months post R3 will be summarised separately within each treatment arm  
32 and exact one sided 95% confidence intervals calculated. The null hypothesis is that the percentage  
33 of participants alive and progression-free at 28 months post R3 is 34.7%. A treatment arm is deemed  
34 a "success" if the one sided 95% confidence intervals of the PFS rate at 28 months excludes 34.71%.  
35 The treatment will then be proposed to be investigated further in a phase III trial.  
36  
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38

39 No multiple imputation is planned for the primary endpoints.  
40  
41

### 42 *Secondary endpoint analyses*

43 Overall survival and other time-to-event endpoints will be analysed using methods similar to those  
44 described for progression-free survival. All binary endpoints will be analysed using similar methods to  
45 those described for the attainment of MRD negativity endpoint.  
46  
47

48 For both R1 and R3, each experimental arm will be independently compared to historical control data  
49 using molecularly matched individual participant data (IPD) from Myeloma XI+(TE) and assessed for  
50 superiority in terms of progression-free survival. Further details of the molecular matching of IPD will  
51 be described in the statistical analysis plan, but it is anticipated that propensity score matching may  
52 be an appropriate technique. In each case a one-sided 10% significance level will be applied for each  
53 comparison with historical data.  
54  
55  
56

57 The number and proportion of participants in each response category will be summarised by allocated  
58 treatment and exact 95% two-sided confidence intervals will be calculated. The difference in  
59  
60

1  
2  
3 proportions for each response category will be presented with corresponding 95% two-sided  
4 confidence intervals.  
5

6  
7 Quality of life will be summarised using mean scores adjusted for baseline and two-sided 95% CI for  
8 each EORTC QLQ-C30 and EORTC QLQ-MY20 module symptom, role and functioning domain at each  
9 assessment time-point. Similar summaries will be produced for quality-adjusted life years (QALYs) as  
10 scored by the EQ-5D 3 Level (EQ-5D-3L) questionnaire. For the key secondary analysis of R1, the Global  
11 Health Status / Quality of Life subscale at two years post-R1, will be compared between the arms using  
12 a multivariable linear regression model, adjusting for the R1 stratification factors.  
13  
14

#### 15 16 *Exploratory and subgroup analyses*

17 A series of subgroup and exploratory analyses will be undertaken. Subgroup analyses will follow the  
18 same structure as the main analysis of the respective endpoint. Where appropriate interaction terms  
19 will be added to the regression models to account for the subgroup being investigated. Subgroup and  
20 exploratory analyses may, by chance, generate false negative or positive results. Those carried out will  
21 be interpreted with caution.  
22  
23

24  
25 The analysis for the exploratory outcomes will be detailed in the SAP.  
26  
27

#### 28 **Health economics**

29 The economic evaluation will take a decision modelling approach to assess the cost-effectiveness of  
30 treatment options for risk stratified treatment vs standard non-stratified treatment over participants'  
31 lifetime. This will allow several research questions to be incorporated within one model. The model  
32 will be developed using best practice[40] and the model structure, health states and parameter values  
33 will be derived from the trial outputs, published literature, and expert clinical opinion. Data to model  
34 stratified treatment options will be drawn from the RADAR trial results while parameters for standard  
35 non-stratified treatment will be obtained from the wider literature.  
36  
37

38  
39 Reflecting the main trial analysis of effectiveness, the economic evaluation will assess the cost-  
40 effectiveness of treatment options at each of the randomisations in RADAR. For standard risk  
41 participants at R1, the cost-effectiveness analysis will compare treatment with isatuximab for 12 cycles  
42 only to long-term isatuximab treatment, continued until disease progression. For standard risk  
43 participants who are MRD-positive at 100 days post-ASCT in terms of conversion to MRD negativity at  
44 R2, the cost-effectiveness of post-ASCT consolidation and maintenance treatments in the treatment  
45 of standard-risk participants will be evaluated. For high-risk participants at R3, the cost-effectiveness  
46 of post-ASCT consolidation and maintenance treatment strategies containing lenalidomide,  
47 bortezomib, dexamethasone and isatuximab separately will be evaluated. In addition, the cost-  
48 effectiveness of stratified treatment pathways will be compared with standard non-stratified  
49 treatments.  
50  
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54  
55 All analyses will be conducted following NICE reference case guidelines[41]. As such, outcomes will be  
56 measured in QALYs based on EQ-5D [42] and EORTC QLQ-C30 [43] utilities and costs will be calculated  
57 from a health and personal social services perspective. Cost-effectiveness will be determined in  
58 comparison to the NICE cost-effectiveness threshold of £20,000 per QALY gained. Deterministic and  
59 probabilistic (using Monte Carlo simulations) sensitivity analyses will be conducted to explore the  
60

1  
2  
3 impact of parameter value changes on estimates of cost-effectiveness and to determine the level of  
4 uncertainty around the results of the lifetime analysis. In addition, value of information analysis will  
5 be conducted to estimate the value of further research.  
6  
7

### 8 **Trial Oversight**

9  
10 The TMG includes the CI, CTRU team and co-investigators that are assigned responsibility for the  
11 clinical set up, ongoing management, promotion of the trial and interpretation of the results. The trial  
12 steering committee (TSC), consisting of independent clinicians and statisticians, will provide overall  
13 supervision on the trial, including trial progress, adherence to protocol, participant safety and  
14 consideration of new information.  
15  
16

### 17 **Data Monitoring**

18  
19 An independent data monitoring and ethic committee (DMEC) will review the safety and ethics of the  
20 trial. Detailed reports will be prepared by the CTRU for the DMEC meetings which will take place at  
21 approximately yearly intervals. Additional reports will also be provided at intervals between these  
22 meetings. The committee will also review cumulative safety data by arm on an ongoing basis along  
23 with individual SAE/SAR listings. After each annual review, the DMEC will make their  
24 recommendations to the TSC about the continuation of the trial.  
25  
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27

### 28 *Interim Analyses*

29  
30 Full interim reports will be presented to the DMEC in confidence annually and following the planned  
31 interim analyses which are expected to take place when half the number of events (119) have been  
32 observed in the treatment de-escalation pathway (R1) and at the end of the activity stage 1 treatment  
33 escalation pathway (R2), approximately 6 months after the 40<sup>th</sup> participant has been randomised.  
34  
35

36  
37 The interim analysis of R1 will be a one-sided test for inferiority conducted at the 5% significance level.  
38 PFS at R1 will be assessed using Cox proportional hazards regression to adjust for the minimisation  
39 factors (excluding centre), and presented using Kaplan-Meier estimates of the survival function.  
40  
41

42  
43 The interim analysis for R2 will be conducted at the end of Stage I (the phase II part) of the  
44 randomisation which is due 6 months following the randomisation of the 40<sup>th</sup> participant. This analysis  
45 will compare each experimental arm with the control arm in separate tests of superiority using a one-  
46 sided 25% significance level and 95% power to determine whether any of the experimental arms show  
47 lack of activity i.e. the null hypothesis in the superiority test is not rejected. Should an arm show lack  
48 of activity it will not be continued to the second stage of the randomisation (the phase III part). To  
49 account for the interim analysis and to give an overall significance level of 1% and power of 80% for  
50 each individual comparison the final analysis will be conducted using a one-sided 1% significance level  
51 and 85% power. Recruitment will continue seamlessly between activity and efficacy in these scenarios.  
52 Formal powered pair-wise comparisons are not undertaken comparing experimental arms at either  
53 stage.  
54  
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56  
57 The DMEC committee members, in light of the interim analysis, will make their recommendations to  
58 the TSC about the continuation of the different aspects of the trial.  
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60

## Harms

### Adverse events

Adverse events are any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs can be defined as any unintentional, unfavourable clinical signs or symptoms; any new illness or disease, or the deterioration of existing disease or illness; or clinically relevant deterioration in any laboratory assessments or clinical test. Due to the nature of multiple myeloma and its treatment, participants are likely to experience several adverse events throughout the course of the disease.

All AEs, both related and unrelated to myeloma treatment will be collected on the relevant eCRF from trial registration until 60 days after the last dose of protocol treatment and will be evaluated in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events 5.0 (NCI-CTCAE). AEs and ARs should continue to be collected for participants who are randomised to 'stop isatuximab' at R1 (and until 60 days after last on-trial assessment), even though they will not be receiving any trial drugs during this period.

### Adverse Events of special interest

An AE of special interest (serious or non-serious) is one of scientific and medical concern specific to isatuximab, for which ongoing monitoring and rapid communication by the investigator to the sponsor is considered to be appropriate. Isatuximab AEs of special interest include;  $\geq$ Grade 3 infusion reactions (IRs), Pregnancies, Symptomatic overdoses with IMP, and Second Primary Malignancies (SPMs).

### Serious adverse events

Serious Adverse Events (SAEs) are defined as any untoward medical occurrence or effect that at any dose results in death; or are life threatening (at the time of the event); or require in-patient hospitalisation or prolongation of existing hospitalisation; or result in persistent or significant disability or incapacity; or result in a congenital anomaly or birth defect; or any other important medical event. All SAEs will be reported from registration until 60 days post the last dose of the trial drug. SAEs should continue to be collected for participants who are randomised to 'stop isatuximab' at R1 (and until 60 days after last on-study assessment), even though they will not be receiving any study drugs during this period.

Serious Adverse Reactions (SARs) are SAEs that are deemed possibly related to any dose administered of any trial treatment. Suspected unexpected serious adverse events (SUSARs) are SARs which are not listed in the reference safety information for that medicinal product. SARs and SUSARs will be reported from the date of first trial dose and for the duration of the trial.

### Secondary malignancies

All new primary malignancies (SPMs) or suspected malignancies occurring from the date of trial registration and for the duration of the trial will be recorded. SPMs will be summarised and reviewed by an appointed member of the TMG who will determine whether trial treatment should continue.

### Pregnancies

Participants registered into RADAR agree to follow the Celgene approved Pregnancy Prevention Programme. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease status) in a female participant must be reported throughout the study and for 12 months after the last dose of cyclophosphamide or for 5 months following cessation of protocol treatment, whichever is longest. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease status) in a male participant's partner must be reported throughout the study and for 6 months after the last dose of cyclophosphamide or for 5 months following cessation of protocol treatment, whichever is longest.

### *Safety Analyses*

Safety analyses will summarise all SUSARs, SARs, SAEs, AEs and ARs, respective to where they occurred within the trial pathway (Induction, ASCT, Pre-R1, Post-R1, Post-R2, Post-R3). Safety data will be presented by treatment group for the safety population in addition to relationship to trial treatment.

### *Auditing*

The CTRU and the trial sponsor have procedures in place to ensure that serious breaches of Good Clinical Practice (GCP) or the trial protocol are picked up and reported. A triggered monitoring plan will ensure that sites at risk are monitored accordingly.

### **Patient and Public Involvement**

RADAR has been developed following extensive discussion with the UK myeloma community. Patients were first involved into the research at the grant application stage, and were incorporated into the development of the primary endpoint of R1, in which they confirmed a research question involving the stopping of treatment given there was no detectable myeloma would be of interest. The trial consent and participant information documents were reviewed for clarity by a patient representative. To ensure that a patient perspective is considered throughout the trial a PPI advisory group, including 4-8 members will feed into TMG meetings, and plan to host quarterly meetings to discuss urgent matters. It is envisioned that the PPI group, may help with writing summaries of results that can be published on patient forums and websites and maybe even shared directly with patients.

### **Ethics and Dissemination**

#### **Research and ethics approval**

Ethics approval has been obtained from the London – Central Research Ethics Committee (20/LO/0238). In addition capacity and capability has been confirmed by the appropriate research and development department for each participating centre prior to opening to participant recruitment into the trial. This included but was not limited to; having access to the non-trial supplied IMP (Bor, Cy and D), being able to conduct FISH as SoC, capacity of staff, ability to complete all protocol required assessments/investigations, and ability to archive trials documents.

Participants will be required to provide informed consent before joining the trial.

## Protocol Amendments

The trial opened to recruitment on 11/05/2021 using protocol version 2, dated 29<sup>th</sup> April 2020. This publication is written based from protocol version 3 dated July 2021. An amendment to protocol version 3 is anticipated Mid-2022, which should include the following:

### *High-Risk Pathway*

The cytogenetic abnormality del(1p) will be added to the definition of high-risk. In addition, Isa will be added to induction regimen for high-risk patients following their first cycle of RCyBorD (whilst their risk status is confirmed). Furthermore, R3 will be removed and high-risk patients will receive RBorIsaD + RIsa only post-ASCT. The pathway will follow a single-arm, single stage, phase II, three outcome design, with the new primary objective to assess the activity of RCyBorD+Isa induction followed by ASCT and RBorD+Isa consolidation and RIsa maintenance in terms of PFS at 18 months post trial registration.

### *Other changes*

- The removal of the phone registration and randomisation;
- The clarification of allowing prescribed medication to remove risks of thromboembolism before preceding onto treatment in the exclusion criteria for registration (and for starting post ASCT treatment)
- The allowance of blood support products, blood transfusions and platelet transfusions as per institutional guidelines at eligibility and pre-treatment assessments
- An update of exclusion criteria to allow for previous plasmacytomas.

## Consent or assent

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any medically qualified person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki. Written consent will be obtained and signed by a medically qualified member of the site research team. Informed consent must be obtained, and the participant must be registered into the trial prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site. This include the confirmation of optional consent (QoL/ Healthcare resource use questionnaires and decision regarding consent for samples to be used in future research). At any stage, participants can withdraw consent without repercussion.

## Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the Data Protection Act 2018.



## Access to data

Individual participant data (with any relevant supporting material, e.g. data dictionary, protocol, statistical analysis plan) for all trial participants (excluding any trial-specific participant opt-outs) will be made available for secondary research purposes at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete.

Data will be shared according to a controlled access approach, based on the following principles:

- The value of the proposal will be considered in terms of the strategic priorities of the CTRU, Chief Investigator and Sponsor, the scientific value of the proposed project, and the resources necessary and available to satisfy any data release request.
- We encourage a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets.
- The timing and nature of any data release must not adversely interfere with the integrity of the trial or research project objectives, including any associated secondary and exploratory research objectives detailed in the ethically approved original research protocol. On an individual trial or research project basis, a reasonable period of exclusivity will be agreed with the trial or research project team.
- Any data release must be lawful, in line with participants' rights and must not compromise patient confidentiality. Where the purposes of the project can be achieved by using anonymised or aggregate data this will always be used. We will release individual patient data only in a form adjusted so that recipients of the data cannot identify individual participants by any reasonably likely means. We will also only share data when there is a binding agreement in place stating that data recipients will not attempt to re-identify any individual participants.
- Any data release must be in line with any contractual obligations to which the CTRU is subject.
- The research must be carried out by a bone fide researcher with the necessary skills and resources to conduct the research project.
- The research project must have clear objectives and use appropriate research methods.
- The research must be carried out on behalf of a reputable organisation that can demonstrate appropriate IT security standards to ensure the data is protected and to minimise the risk of unauthorised disclosure.

Data will only be shared for participants who have given consent to use of their data for secondary research.

Requests to access trial data should be made to [CTRU-DataAccess@leeds.ac.uk](mailto:CTRU-DataAccess@leeds.ac.uk) in the first instance. Requests will be reviewed (based on the above principles) by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

## Ancillary and post-trial agreements

Participants who stop trial treatment due to progression or any point prior to the end of trial will be treated off-trial at the discretion of their treating clinician. Those who stop prior to disease progression will be followed up 2 monthly until disease progression, death or the end of the trial. Following disease progression all participants will be followed up annually until death, or until the end of the trial for post progression endpoints.

Participants in the R1 pathway who are MRD-positive at 12 months post 12 cycles of isatuximab and therefore aren't eligible for randomisation 1 will continue to receive isatuximab maintenance, these

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2  
3 participants would continue to be monitored, and data collected, as previously but trial samples would  
4 not be collected.  
5

### 6 7 **Dissemination policy**

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9 Authorship will be in keeping with the UK-MRA publication policy and due acknowledgement to  
10 participants, local investigators, funders and NCRI Haematological Oncology Study Group support  
11 made. The success of the trial depends upon the collaboration of all participants. For this reason, credit  
12 for the main results will be given to all those who have collaborated in the trial, through authorship  
13 and contributor-ship. Uniform requirements for authorship for manuscripts submitted to medical  
14 journals will guide authorship decisions alongside the guidance of the UK Myeloma Research Alliance  
15 Authorship Policy.  
16  
17

18  
19 To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial or  
20 a primary endpoint being reached, either for trial publication or oral presentation purposes, without  
21 the permission of the Trial Steering Committee and the (Co-)Chief Investigators. In addition, individual  
22 collaborators must not publish data concerning their participants that is directly relevant to the  
23 questions posed in the trial until the main results of the trial have been published and following  
24 written consent from the Sponsor.  
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27

### 28 **Appendices**

#### 29 30 *Informed consent material*

31  
32 The consent forms which are to be completed by the participant at Bone Marrow Registration and/or  
33 Trial Registration and prior to each randomisation pathways are included in supplementary material.  
34  
35

#### 36 *Biological specimens*

37  
38 The collection of central samples for laboratory analysis is summarised in Figures 3 and 4. The analysis  
39 to be conducted for trial purposes is stated in the supplementary material. Additional analysis may be  
40 carried out by each central laboratory provided the appropriate consent for sample use in future  
41 research has been provided by the participant at trial entry.  
42  
43

### 44 **Author Contributions**

45  
46 The RADAR trial was conceived by KY and MC and designed by them in collaboration with DAC. All  
47 authors (KLR, ABC, KR, DAC, AH, SQ, MD, MK, RO, HWA, GC, DM, CO, LB, RL, AP, BD, MC, GP, RP, GJ,  
48 CB, JS, RT, AC, CP, MC, SA, and KY) inputted into the development of the protocol and participant  
49 information sheet. The first draft of the protocol paper was written by KLR and ABC. All authors (KLR,  
50 ABC, KR, DAC, AH, SQ, MD, MK, RO, HWA, GC, DM, CO, LB, RL, AP, BD, MC, GP, RP, GJ, CB, JS, RT, AC,  
51 CP, MC, SA, and KY) reviewed and approved the final manuscript.  
52  
53

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55  
56 This trial is funded by Cancer Research UK (C9203/A24078), Sanofi Genzyme and Celgene: A BMS  
57 Company. The funders had no role in the design, collection, analysis or collection of data; in writing  
58  
59  
60

1  
2  
3 the manuscript; or in the decision to submit the manuscript for publication. This work was also  
4 supported by Core Clinical Trials Unit Infrastructure from Cancer Research UK (C7852/A25447).  
5  
6

7 The trial sponsor is responsible for the overall conduct of the trial as defined by Directive 2001/20/EC  
8 is University of Leeds, UoL/LTHT Joint Sponsor QA office (CTIMPs); Research & Innovation  
9 Centre/Faculty of Medicine & Health; Leeds Teaching Hospitals NHS Trust/University of Leeds; St  
10 James University Hospital; Leeds LS9 7TF.  
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### 14 **Competing Interest Statement**

15  
16 ABC, KLR, DAC, AH, CO, LBai, LBar, AP, RL report grants and non-financial support from BMS/Celgene,  
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18 Amgen, grants and non-financial support from Takeda, during the conduct of the trial. DAC also  
19 reports travel support from Celgene Corporation.  
20  
21  
22

23 KY, RDT, CB, GJ, GP, MC, BD, DM, GC, HA, KR,SA, AC have no conflicting interests to declare. MC  
24 declares, Bristol Myers Squibb- employee, Honoraria/travel support in the last 3 years from, Amgen  
25 ,BMS/Celgene, Janssen, Takeda, Abbvie. CP declares BMS/Celgene Ad boards and speaker fees, Sanofi  
26 – Ad board, speaker fees, conference registration fees. JS reports Carrying out consultancy work  
27 (Advisory Board) for Sanofi. And an educational speaking engagement for Celgene/BMS RP declares;  
28 Honoraria – Janssen, BMS, Abbvie, GSK. Consultancy: GSK, Janssen. Meeting support: Janssen,  
29 Takeda, BMS. RO declares- Janssen - advisory board, honoraria, Celgene – honoraria, Beigene -  
30 advisory board, honoraria, Astra Zeneca – honoraria. MK declares inter-relationships: AbbVie:  
31 consultancy; Amgen: honoraria; BMS/Celgene: consultancy, research funding (institution); GSK:  
32 consultancy; Janssen: consultancy, research funding (institution); Karyopharm: consultancy; Pfizer:  
33 consultancy; SeattleGenetics: consultancy; Takeda: consultancy; Sanofi: honoraria. MD reports  
34 owning stock in Abingdon Health. SQ is the founder and CSO of Achilles therapeutics a company  
35 developing T cell therapies for solid tumours.  
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3 **Figure Legends/ Captions**

4 Figure 1: Flow chart of participant’s timelines in the RADAR study

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6 Figure 2: Schedule of local investigations

7 Figure 3: Central Investigations from diagnosis up to 100 days post-ASCT

8 Figure 4: Central Investigations for the R1, R2 and R3 pathways  
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For peer review only

Figure 1: Flowchart of Participants timelines in the RADAR Study

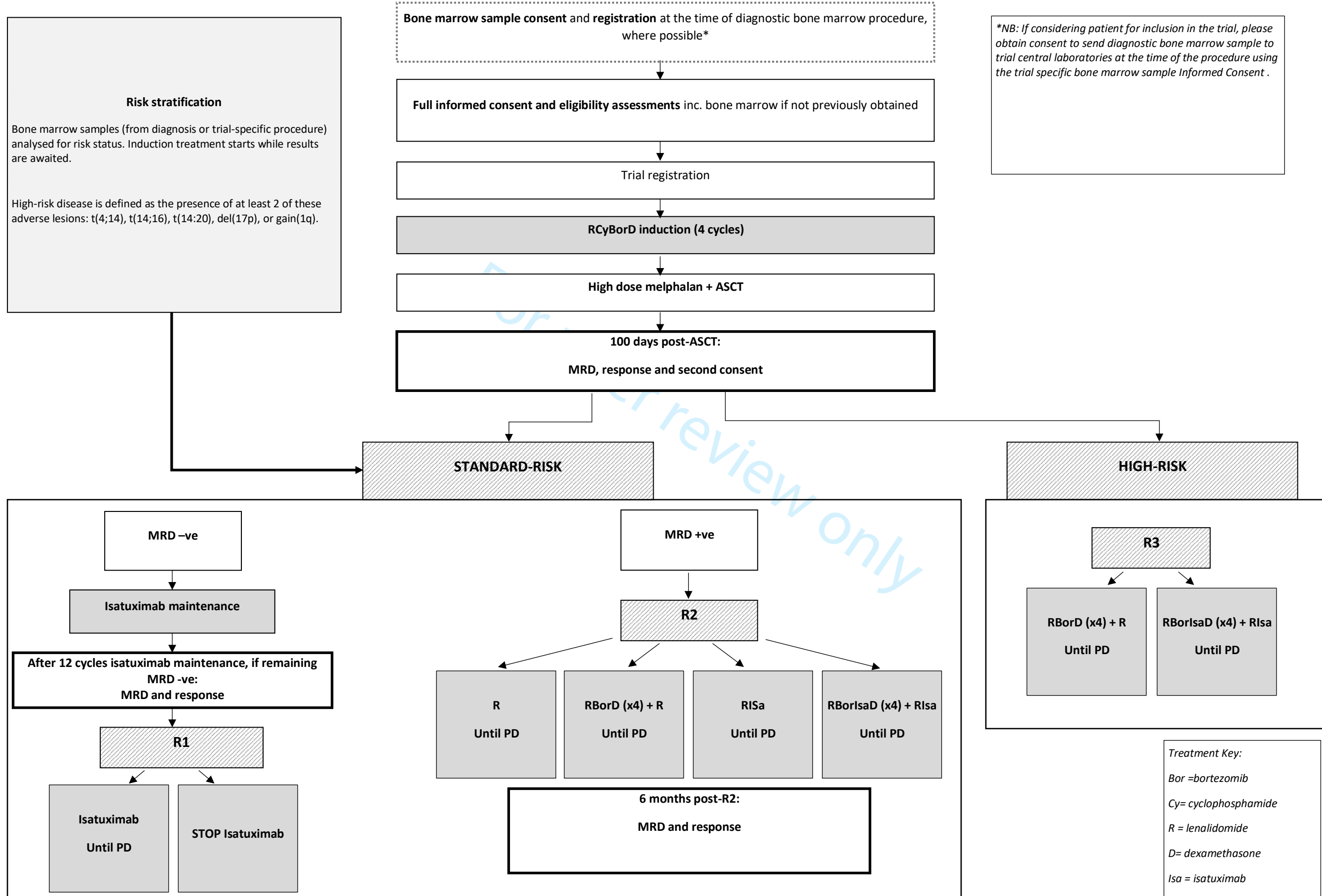




Figure 2: Schedule of Local Investigations

	RCyBorD Induction – All participants				R1 treatment pathway			R2 and R3 treatment pathway R2 participants on R or R1sa arm: After 3,6,12 and 18 cycles**		
	Pre-registration/baseline (within 14 days prior to registration, unless otherwise stated)	Day 1 (or day -1) of each cycle during RCyBorD induction††	End of RCyBorD induction	100 days post-ASCT (within 14 days prior to R2, start of Isatuximab maintenance or R3)	Day 1 of each cycle of isatuximab treatment††	On the day of isatuximab dose††	Follow up for participants coming off study during R1 treatment pathway: every 2 months	Day 1 of each cycle of treatment††	On day of (and prior to) every isatuximab dose††	Follow up for participants coming off study during R2/R3 treatment pathway: every 2 months
Written informed consent	✓ Consent to be taken prior to all assessments, permitted outside the 14-day window			✓ (permitted outside the 14-day window)						
Physical examination	✓	✓	✓	✓	✓			✓		
ECOG	✓	✓	✓	✓	✓			✓		
Covid vaccination status	✓	✓	✓	✓	✓		✓	✓		✓
Medical history (including review for prior cancers and history of Covid infection)	✓		✓	✓						
Assessment of cardiac risk*	✓(results from formal measurements within 28 days prior to registration)	If clinically indicated	✓	If clinically indicated	If clinically indicated			If clinically indicated		
ECG					Every 3 months in participants receiving Isatuximab			Every 3 months in participants receiving Isatuximab		
Thyroid function monitoring*	✓(within 28 days prior to registration)	If clinically indicated	✓	If clinically indicated	If clinically indicated			If clinically indicated		
FBC, LFTs, albumin, LDH, U&Es, calcium, and creatinine¶	✓	✓	✓	✓	✓	✓ FBC, U&E and creatinine only		✓	✓ FBC, U&E and creatinine only	
Hepatitis B, (surface antigen and core antibody), ,hepatitis C and HIV	⊠(within 28 days prior to registration)									
β2-microglobulin (β2M)	✓									
C-Reactive protein (CRP)	✓									
Calculated creatinine clearance (using Cockcroft-Gault formula)	✓	✓	✓	✓	✓			✓		
Serum paraprotein and immunofixation, serum free light chains and urinary free light chain detection	✓	✓	✓	✓	✓		✓ (if performed as part of standard care)	✓		✓ (If performed as standard of care)
Bone marrow (aspirate and trephine) See Table below for details of central investigations	✓ (within 6 weeks prior to registration)	✓(recommended only if a first occurrence of CR or SCR is suspected)	✓	✓	✓(recommended only if a first occurrence of CR or sCR is suspected)		✓ (if performed as part of standard care)	✓ (recommended only if first occurrence of CR/SCR is suspected)		✓ (If performed as standard of care)
Pregnancy prevention counselling	✓	At least every 28 days during lenalidomide treatment								
Pregnancy test† (for females of childbearing potential)	✓	✓‡			✓				✓‡	
Cross-sectional imaging according to local practice, to include the thorax (low dose whole body CT recommended)	Within 3 months before registration§	If clinically indicated. †			If clinically indicated			If clinically indicated		
Assessment of adverse events (including adverse events and second primary malignancy)		Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose)			Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose) . AEs should continue to be monitored for participants randomised to 'stop Isatuximab' at R1 (and until 60 days after last on-study assessment).			Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose)		

\*Performed as part of standard of care.  
\*\* ECGs should be scheduled to align with other required face-to-face visits  
¶ The FBC should be repeated mid-cycle 1 (Day 14 +/-3 days) or more frequently and during subsequent cycles if there is a concern about cytopenias  
† Females of childbearing potential (FCBP) must have a negative pregnancy test performed by a healthcare professional in accordance with the Celgene Lenalidomide Pregnancy Prevention Plan  
‡‡ May be performed within the 48 hours prior to the specified day  
‡‡‡ In addition to standard Day 1 assessments  
‡ All FCBP: The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide.  
FCBP with regular or no menstrual cycles: within 24 hours before start of lenalidomide treatment; weekly for the first 28 days of study participation; 4-weekly as a minimum during lenalidomide treatment; at study discontinuation; and 4 weeks after last dose of lenalidomide  
FCBP with irregular menstrual cycles: within 24 hours before start of lenalidomide treatment; weekly for the first 28 days of study participation; 2-weekly as a minimum during lenalidomide treatment; at study discontinuation; and at 2 and 4 weeks after last dose of lenalidomide

**N.B. During the COVID-19 pandemic, face-to-face assessments must be carried out at least at the beginning of cycles 1 and 2 and at the end of consolidation. Subsequently, participants must be seen by a clinician at least every 3 cycles (and more frequently if clinically indicated or there are concerns).**

Figure 3: Central Investigations from diagnosis up to 100 days post-ASCT

Sample	Investigation	Diagnosis (if patient consented on NHS form and trial bone marrow Informed Consent Document) <sup>1</sup>	Baseline (post trial consent and before the start of treatment)	Day 1 of Cycle 1 RCyBorD induction	End of induction cycle 1	End of induction cycle 2	End of RCyBorD induction	100 days post-ASCT and prior to consolidation/maintenance
0.5-1 mL EDTA bone marrow aspirate <b>SEND TO HMDS, LEEDS</b>	Minimal Residual Disease	✓	✓ (if not sent previously)				✓	✓
10 mL clotted peripheral blood Random urine sample <b>SEND TO BIRMINGHAM</b>	Disease parameters (including paraproteins) for response assessments and covid-19 antibody response M-protein interference assay		✓	✓ Only if baseline sample not within 14 days	✓	✓	✓	✓
10 mL EDTA bone marrow aspirate 10 mL blood <b>SEND TO UCL, LONDON</b>	Tumour DNA for neoantigens cfDNA Immune profiling	✓ Bone marrow only	✓ BMA (if not sent previously) & blood	✓ Cycle 1 only 10 mL blood (only if baseline sample is not from within 14 days prior to cycle 1 day 1)				✓
Bone marrow trephine (6 sections) <b>SEND TO UCL, LONDON</b>	Immunostaining for immune function	✓	✓ (if not sent previously)					✓

Trial consent  
Consented to Myeloma XV trial and central laboratory investigations

<sup>1</sup> Baseline bone marrow samples may be taken before trial consent, provided that patients have consented to these samples being taken using the standard NHS consent form. The patient must have provided written informed trial consent on the trial bone marrow Informed Consent Document before these samples can be sent to the central laboratories.

Figure 4: Central Investigations for the R1, R2 and R3 pathways

Sample	Investigation	Standard-risk MRD-negative participants (R1 pathway)	Standard-risk MRD-positive participants on R or R1sa arm (R2 pathway)			Standard-risk MRD-positive participants on RBorD+R or RBor1saD+R1sa arm (R2 pathway)			High-risk participants (R3 pathway)			All participants
			After cycle 3	After cycles 6, 12 and 18	After cycle 24	After consolidation cycle 4	After maintenance cycles 3, 9 and 15	After maintenance cycle 21	After consolidation cycle 4	After maintenance cycles 3, 9 and 15	After maintenance cycle 21	
		After cycles 6, 12 and 24 of maintenance (or at equivalent time-points if randomised to stop receiving 1sa)										Disease progression
0.5-1 mL EDTA bone marrow aspirate SEND TO HMDS, LEEDS	Minimal Residual Disease	✓	✓	✓		✓	✓		✓	✓		✓
10 mL clotted peripheral blood Random urine sample SEND TO BIRMINGHAM	Disease parameters (including paraproteins) for response assessments and covid-19 antibody response M-protein interference assay	✓	✓	✓	✓ (blood only)	✓	✓	✓ (blood only)	✓	✓	✓ (blood only)	✓
10 mL EDTA bone marrow aspirate 10 mL blood SEND TO UCL, LONDON	Tumour DNA for neoantigens cfDNA Immune profiling	✓ (only after 6 cycles)	✓			✓			✓			✓
Bone marrow trephine SEND TO UCL, LONDON	Immuno-chemistry for immune function		✓			✓			✓			✓

## **RADAR: Protocol Paper Attachments**

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## 1 Glossary of Terms

1		
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6	AE	Adverse event
7	ALT	Alanine aminotransferase
8	ANC	Absolute neutrophil count
9	AR	Adverse reaction
10	ASCT	Autologous stem cell transplantation
11	β2M	Beta2-microglobulin
12	BD	Twice daily
13	CI	Chief Investigator
14	CR	Complete response
15	CRF	Case report form
16	CRUK	Cancer Research United Kingdom
17	CTCAE	Common Terminology Criteria for Adverse Events
18	CTRU	Clinical Trials Research Unit
19	Cy	Cyclophosphamide
20	D	Dexamethasone
21	DMEC	Data Monitoring and Ethics Committee
22	DSUR	Developmental Safety Update Report
23	ECOG	Eastern Cooperative Oncology Group
24	eCRF	Electronic Case Report Form
25	EORTC	European Organisation for Research and Treatment of Cancer
26	FISH	Fluorescence in situ hybridization test
27	FWER	Family-wise error rate
28	GCP	Good Clinical Practice
29	HDM	High-dose melphalan
30	HMDs	Haematological Malignancy Diagnostic Service
31	IMiD®	Immunomodulatory Drug
32	IMP	Investigational medicinal product
33	IMWG	International Myeloma Working Group
34	IPD	Individual participant data
35	Isa	Isatuximab
36	ISS	International Staging System
37	ITT	Intention to treat
38	LFT	Liver function test
39	MedDRA	Medical Dictionary for Regulatory Activities
40	mg	Milligram
41	MGUS	Monoclonal gammopathy of undetermined significance
42	MHRA	Medicines and Healthcare Products Regulatory Agency
43	MM	Multiple myeloma
44	MR	Minimal response
45	MRD	Minimal Residual Disease
46	NCRI	National Cancer Research Institute
47	NDMM	Newly diagnosed multiple myeloma
48	NICE	National Institute for Health and Care Excellence
49	OS	Overall survival
50	PD	Progressive disease
51	PFS	Progression-free survival
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3	PFS2	Time to second progression
4	PI	Principal Investigator
5	PIS	Patient Information Sheet
6	PP	Paraprotein
7	PR	Partial response
8	PS	Performance status
9	QoL	Quality of life
10	R	Lenalidomide
11	R1-3	Randomisation 1-3
12	RCT	Randomised controlled trials
13	RDE	Remote Data Entry
14	REC	Research Ethics Committee
15	R-ISS	Revised International Staging System
16	RSI	Reference Safety Information
17	SC	Sub-cutaneous
18	SD	Stable disease
19	SAE	Serious adverse event
20	SAP	Statistical analysis plan
21	SAR	Serious adverse reaction
22	SmPC	Summary of Product Characteristics
23	SOP	Standard operating procedure
24	SPM	Secondary Primary Malignancy
25	SSOP	Study site operating procedure
26	SUSAR	Suspected unexpected serious adverse reaction
27	TE	Transplant eligible
28	TMG	Trial Management Group
29	TNE	Transplant non-eligible
30	TSC	Trial Steering Committee
31	U&Es	Urea & electrolytes
32	UK-MRA	United Kingdom Myeloma Research Alliance
33	ULN	Upper limit of normal
34	VGPR	Very good partial response
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## 2 List of Sites in the RADAR Trial

Aberdeen Royal Infirmary	Royal Bournemouth Hospital	University Hospital Wishaw
Royal Sussex County Hospital	Poole General Hospital	St Richard's Hospital
Chesterfield Royal Hospital	Salisbury District Hospital	Worthing Hospital
Derriford Hospital	Sunderland Royal Hospital	The Christie
Kent & Canterbury Hospital, Canterbury	South Tyneside District Hospital	Cheltenham General Hospital
Queen Elizabeth the Queen Mother Hospital	Southmead Hospital Bristol	Gloucestershire Royal Hospital
William Harvey Hospital	St. Helens	The Clatterbridge Centre
Freeman Hospital	Whiston Hospital	
Queen Elizabeth Hospital Gateshead	St George's Hospital (Tooting)	
Hammersmith Hospital	Torbay Hospital	
Manchester Royal Infirmary	University College London Hospital	
Wythenshawe Hospital	Leicester Royal Infirmary	
Milton Keynes University Hospital	Worcestershire Royal Hospital	
Perth Royal Infirmary	Alexandra Hospital, Redditch	
Ninewells Hospital	York Hospital	
Northampton General Hospital	University Hospital of Wales, Cardiff	
Churchill Hospital	Stratford Hospital	
Horton General Hospital	Warwick Hospital	
Queen Alexandra Hospital, Portsmouth	New Cross Hospital	
Queen Elizabeth Hospital, Birmingham	University Hospital Coventry	
Raigmore Hospital, Inverness	University Hospital Monklands	
Rotherham General Hospital	University Hospital Hairmyres	

### 3 Spirit Checklist: Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	1,2,3
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	<a href="#">#3</a>	Date and version identifier	29
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	32
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1, 31
Roles and responsibilities: sponsor contact information	<a href="#">#5b</a>	Name and contact information for the trial sponsor	31,32
Roles and responsibilities: sponsor and funder	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	32
Roles and responsibilities: committees	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	26,27
<b>Introduction</b>			
Background and rationale	<a href="#">#6a</a>	Description of research question and justification for undertaking the trial, including summary of relevant	6,7



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3		studies (published and unpublished) examining	
4		benefits and harms for each intervention	
5			
6	Background and	<a href="#">#6b</a> Explanation for choice of comparators	6,7
7	rationale: choice of		
8	comparators		
9			
10	Objectives	<a href="#">#7</a> Specific objectives or hypotheses	7, 18
11			
12	Trial design	<a href="#">#8</a> Description of trial design including type of trial (eg,	8
13		parallel group, crossover, factorial, single group),	
14		allocation ratio, and framework (eg, superiority,	
15		equivalence, non-inferiority, exploratory)	
16			
17	<b>Methods:</b>		
18	<b>Participants,</b>		
19	<b>interventions, and</b>		
20	<b>outcomes</b>		
21			
22			
23	Study setting	<a href="#">#9</a> Description of study settings (eg, community clinic,	8
24		academic hospital) and list of countries where data	
25		will be collected. Reference to where list of study sites	
26		can be obtained	
27			
28	Eligibility criteria	<a href="#">#10</a> Inclusion and exclusion criteria for participants. If	8-14
29		applicable, eligibility criteria for study centres and	
30		individuals who will perform the interventions (eg,	
31		surgeons, psychotherapists)	
32			
33			
34	Interventions:	<a href="#">#11a</a> Interventions for each group with sufficient detail to	15-17
35	description	allow replication, including how and when they will be	
36		administered	
37			
38	Interventions:	<a href="#">#11b</a> Criteria for discontinuing or modifying allocated	17
39	modifications	interventions for a given trial participant (eg, drug	
40		dose change in response to harms, participant	
41		request, or improving / worsening disease)	
42			
43			
44	Interventions:	<a href="#">#11c</a> Strategies to improve adherence to intervention	17
45	adherence	protocols, and any procedures for monitoring	
46		adherence (eg, drug tablet return; laboratory tests)	
47			
48	Interventions:	<a href="#">#11d</a> Relevant concomitant care and interventions that are	17
49	concomitant care	permitted or prohibited during the trial	
50			
51	Outcomes	<a href="#">#12</a> Primary, secondary, and other outcomes, including the	18
52		specific measurement variable (eg, systolic blood	
53		pressure), analysis metric (eg, change from baseline,	
54		final value, time to event), method of aggregation (eg,	
55		median, proportion), and time point for each	
56		outcome. Explanation of the clinical relevance of	
57		chosen efficacy and harm outcomes is strongly	
58		recommended	
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2				
3	Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18,19
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8	Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
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13	Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	23
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17	<b>Methods:</b>			
18	<b>Assignment of</b>			
19	<b>interventions (for</b>			
20	<b>controlled trials)</b>			
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22	Allocation: sequence generation	<a href="#">#16a</a>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	23
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31	Allocation concealment mechanism	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	23
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37	Allocation: implementation	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	23
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41	Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
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45	Blinding (masking): emergency unblinding	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
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50	<b>Methods: Data</b>			
51	<b>collection,</b>			
52	<b>management, and</b>			
53	<b>analysis</b>			
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55	Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires,	23
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3		laboratory tests) along with their reliability and	
4		validity, if known. Reference to where data collection	
5		forms can be found, if not in the protocol	
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7	Data collection plan: retention	<a href="#">#18b</a> Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	23
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12	Data management	<a href="#">#19</a> Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	23
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20	Statistics: outcomes	<a href="#">#20a</a> Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
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26	Statistics: additional analyses	<a href="#">#20b</a> Methods for any additional analyses (eg, subgroup and adjusted analyses)	24
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29	Statistics: analysis population and missing data	<a href="#">#20c</a> Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	24
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34	<b>Methods:</b>		
35	<b>Monitoring</b>		
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37	Data monitoring: formal committee	<a href="#">#21a</a> Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	27
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46	Data monitoring: interim analysis	<a href="#">#21b</a> Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	27
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52	Harms	<a href="#">#22</a> Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	27
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57	Auditing	<a href="#">#23</a> Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	29
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## Ethics and dissemination

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3	<b>Ethics and</b>			
4	<b>dissemination</b>			
5				
6	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee /	29
7	approval		institutional review board (REC / IRB) approval	
8				
9	Protocol	<a href="#">#25</a>	Plans for communicating important protocol	29
10	amendments		modifications (eg, changes to eligibility criteria,	
11			outcomes, analyses) to relevant parties (eg,	
12			investigators, REC / IRBs, trial participants, trial	
13			registries, journals, regulators)	
14				
15	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from	30
16			potential trial participants or authorised surrogates,	
17			and how (see Item 32)	
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20	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	30,31
21	ancillary studies		participant data and biological specimens in ancillary	
22			studies, if applicable	
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24	Confidentiality	<a href="#">#27</a>	How personal information about potential and	30
25			enrolled participants will be collected, shared, and	
26			maintained in order to protect confidentiality before,	
27			during, and after the trial	
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30	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	32
31	interests		investigators for the overall trial and each study site	
32				
33	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial	30
34			dataset, and disclosure of contractual agreements that	
35			limit such access for investigators	
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37	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and	32
38	trial care		for compensation to those who suffer harm from trial	
39			participation	
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41	Dissemination	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate	31
42	policy: trial results		trial results to participants, healthcare professionals,	
43			the public, and other relevant groups (eg, via	
44			publication, reporting in results databases, or other	
45			data sharing arrangements), including any publication	
46			restrictions	
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49	Dissemination	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use	31
50	policy: authorship		of professional writers	
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52	Dissemination	<a href="#">#31c</a>	Plans, if any, for granting public access to the full	31
53	policy: reproducible		protocol, participant-level dataset, and statistical code	
54	research			
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57	<b>Appendices</b>			
58	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation	(Supplementary
59	materials		given to participants and authorised surrogates	Material)
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3 Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage (Supplementary  
4 of biological specimens for genetic or molecular Material)  
5 analysis in the current trial and for future use in  
6 ancillary studies, if applicable  
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8 None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative  
9 Commons Attribution License CC-BY-NC. This checklist can be completed online using  
10 <https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)  
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For peer review only

#### 4 Excluded Concomitant Medication:

##### Excluded concomitant Medication:

1. Systemic treatment with any of the following metabolising enzyme inducers and inhibitors should be avoided, unless there is no appropriate alternative medication for the participant's use (if there were to be a drug-drug interaction with an inducer, cyclophosphamide and bortezomib metabolite exposure would be increased):
  - a. Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
  - b. Strong CYP3A inhibitors
2. Excluded foods and dietary supplements include St. John's Wort, green tea and supplements containing green tea extracts
3. The following medicinal products and procedures are **prohibited** during this study:
  - a. Any antineoplastic treatment with activity against MM, other than study drugs
  - b. Platelet transfusions within 3 days prior to study drug dosing for any dosing day, or prior to randomisation in order to meet eligibility criteria.
  - c. Additional steroid therapy (not as trial IMP) (except before commencing trial treatment up to a maximum of 160mg dexamethasone equivalent as per inclusion criteria or steroids used to manage hypersensitivity to trial medication)
  - d. Radiotherapy for the treatment of symptoms related to disease progression.
  - e. Continuous use of clarithromycin (short courses of 5-10 days are permitted for treatment of infective episodes when indicated)
  - f. Hormone replacement therapy and erythropoietic agents and other agents that increase the risk of thrombosis (applicable during treatment with lenalidomide)

## ***Quality of Life and Health Economics questionnaires***

### **Timepoints for all participants up to 100 days post-ASCT**

- Baseline
- End of induction
- 100 days post-ASCT

### **\*R1 pathway participants**

- After cycles 6, 12, 24 and 36 (for participants randomised to 'stop isatuximab' at R1, the cycle 24 and 36 questionnaires should still be completed at equivalent timepoints)

### **\*Timepoints for R2 and R3 pathway participants receiving R or RIsa**

- After cycles 6, 12 and 24 of maintenance

### **\*Timepoints for R2 and R3 pathway participants receiving RBorD+R or RBorIsaD+RIsa**

- After cycles 3, 9 and 21 of maintenance.

*\*Note that participants who stop trial treatment should complete QoL at the equivalent time points (unless the participant wishes to withdraw consent for any further data collection)*

## 5 Exploratory analysis

Exploratory analysis will consider; the effect of post-ASCT consolidation regimens utilising combinations of lenalidomide, bortezomib, dexamethasone, and isatuximab on immune function in the bone marrow of participants following ASCT, using high dimensional characterisation of the immune microenvironment, immune subsets, phenotype and transcriptome; T cell receptor (TCR) repertoire in the bone marrow of participants following ASCT and consolidation and/or maintenance; correlation of baseline immune profile, TCR diversity and function with disease response, including MRD status and timing of disease relapse; ex-vivo functional studies with participant derived samples used to generate explants or immune-competent patient derived xenografts (icPDX); and to review infection and re-infection rates of COVID-19 in participants during induction, post-ASCT and during post-ASCT consolidation and maintenance treatment. All exploratory analysis to be conducted by the trial statisticians will be pre-specified in the statistical analysis plan.



## 6 Subgroup analysis

Subgroup analysis will be conducted to determine whether a selection of patient characteristics, haematology / local serological results, biochemistry results and cytogenetic/molecular results as well as response assessments (full list below) are prognostic of the endpoints; PFS, PFS2, OS, attainment of  $\geq$ VGPR and attainment of MRD negativity, as defined for all randomisations. Note that the subgroups listed under the Response subheading will not be analysed for the last two endpoints.

### Patient Characteristics

- Age (years) at trial registration ( $\leq 65$ ,  $>65$ )
- Sex (Male / Female)
- ECOG performance status at trial registration (0, 1,  $\geq 2$ )
- ISS at trial registration (Stage I, Stage II, Stage III)
- R-ISS at trial registration (Stage I, Stage II, Stage III)

### Haematology / Local Serological Results

- Haemoglobin concentration at trial registration ( $<100$ ,  $\geq 100$  g/L)
- Platelets at trial registration ( $<150$ ,  $\geq 150 \times 10^9$ /L)
- White blood cells at trial registration ( $< LLN$  (Lower limit of normal),  $\geq LLN$ )
- Neutrophil count at trial registration ( $< LLN$ ,  $\geq LLN$ )
- Lymphocyte count at trial registration ( $< LLN$ ,  $\geq LLN$ )
- Plasma cells (%) in bone marrow at trial registration ( $<60\%$ ,  $\geq 60\%$ )

### Biochemistry Results

- $\beta$ -2 microglobulin concentration at trial registration ( $<3.5$ ,  $3.5$ – $<5.5$ ,  $\geq 5.5$  mg/L)
- Serum creatinine concentration at trial registration ( $<175$ ,  $\geq 175$   $\mu$ mol/L)
- Corrected serum calcium concentration at trial registration ( $<2.75$ ,  $\geq 2.75$  mmol/L)
- Serum albumin at trial registration ( $<ULN$  (Upper limit of normal) ,  $\geq ULN$ )
- Lactate dehydrogenase at trial registration ( $<ULN$ ,  $\geq ULN$ )
- C-Reactive protein at trial registration ( $<ULN$ ,  $\geq ULN$ )
- Serum bilirubin at trial registration ( $<ULN$ ,  $\geq ULN$ )
- ALT/AST at trial registration ( $<ULN$ ,  $\geq ULN$ )

### Cytogenetic/molecular Results

- t(4,14) at trial registration (detected, not detected)
- t(14,16) at trial registration (detected, not detected)
- t(14,20) at trial registration (detected, not detected)
- del(17p) at trial registration (detected, not detected)
- 1q gain at trial registration (detected, not detected)
- Hyperdiploidy at trial registration (detected, not detected)
- The number of high-risk adverse lesions at trial registration (R1 and R2: 0, 1 unable to determine, R3: 2,  $\geq 3$ , or unable to determine)

### Response

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3 - Response to RCyBorD induction (<VGPR, ≥ VGPR)  
4 - Response at 100 days post-ASCT (<VGPR, ≥ VGPR)  
5  
6 - Response at the end of consolidation (<VGPR, ≥ VGPR)  
7 - Response to 12m post-ASCT treatment (<VGPR, ≥ VGPR)  
8 - MRD response to RCyBorD induction (R3 Only: MRD positive, MRD Negative)  
9 - MRD at 100 days post-ASCT (R3 Only: MRD positive, MRD negative)  
10 - MRD response to 6m post-ASCT treatment (R3 Only: MRD positive, MRD Negative)  
11 - MRD response to 12m post-ASCT treatment (R3 Only MRD positive, MRD Negative)  
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15 Further subgroup analyses may be undertaken, as appropriate and all the subgroups will be fully  
16 defined within the statistical analysis plan according to the current criteria [1-3].  
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## 7 Informed Consent Material

### *Bone Marrow Consent*

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number :
EudraCT Number:	Principal Investigator:



## **RADAR (UK-MRA Myeloma XV)**

### **INFORMED CONSENT DOCUMENT FOR BONE MARROW AND BLOOD SAMPLE**

**Please initial  
each box**

1. I confirm that I have read and understand the information sheet for the bone marrow sample request and have had the opportunity to ask questions.
2. I understand that my providing bone marrow samples is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected.
3. I understand that the samples will be sent along with information about me, which will include NHS number or CHI number for Scotland and may include my name.
4. I agree to these samples being stored and used for research investigations that form part of the RADAR study, and understand that this will include genetic research (for example, analysis of DNA).

- 5. I understand that a unique reference number will be allocated to the samples which may allow them to be linked back to me in future for research purposes.
- 6. I understand that my data may be shared on a collaborative basis with researchers in the UK and potentially, centres abroad.
- 7. I agree to allow any information provided to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible.
- 8. I understand that results of my laboratory tests may be shared with other research teams if I am taking part in another clinical study being run by the University of Leeds.
- 9. I agree to a copy of this Consent Form being sent to the Clinical Trials Research Unit.
- 10. I agree for my details (which will include date of birth and NHS number or CHI number for Scotland) to be submitted to NHS Digital or other central UK NHS bodies so that information about my health, and mortality should this become available, may be obtained by the CTRU if necessary.
- 11. I agree to provide bone marrow samples.

**Please indicate your wishes in the below scenarios:**

A) If I am diagnosed with a plasma cell dyscrasia, other than myeloma, I give permission for the samples sent to the central laboratories to be stored and used in future research that receives ethical approval. I understand that the samples and data collected from them may be shared with researchers, possibly in other countries.

**Please initial**

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

B) If I am diagnosed with myeloma but do not take part in the RADAR study, I give permission for the samples sent to the central laboratories to be stored and used in future research that receives ethical approval. I understand that the samples and data collected from them may be shared with researchers, possibly outside the EEA.

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

**Patient (to be completed by the patient):**

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the request to the above named patient and he/she has indicated his/her willingness for samples of bone marrow to be sent to the RADAR laboratories.

Signature.....

Name (block capitals).....

Date.....

**(If used)Translator:**

Signature.....

Name (block capitals).....

Date.....

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

For peer review only

**Part A: Initial Treatment and Further Study Consent**

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)**

**INFORMED CONSENT DOCUMENT PART A**

**Initial Treatment and Further Study Information**

PLEASE INITIAL EACH BOX

- 12. I confirm that I have read and understand the Part A information document for the RADAR study and have had the opportunity to ask questions.
- 13. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. I understand that even if I withdraw from the above study, the data and samples collected from me will be used in analysing the results of the study, and in some cases further information about any unwanted effects of my treatment may need to be collected by the study team.
- 14. I understand that my healthcare records may be looked at by authorised individuals from the study team, regulatory bodies or Sponsor in order to check that the study is being carried out correctly.
- 15. I am aware that I am required to have samples taken and sent to laboratories and I understand that this will include genetic research (for example, analysis of DNA). I understand that the samples will be sent along with information about me, which will include NHS number, or CHI number for Scotland, and may include my name.

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16. I understand that results or reports from imaging scans, blood tests or other investigations (including for additional cancers) may be sent to the Clinical Trials Research Unit for central review by the research team.
17. I agree to allow any information or results arising from this study to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible.
18. I understand that my data and results of my laboratory tests (blood, urine and bone marrow sample collections) may be shared with other research teams if I am taking part in another clinical study being run by the University of Leeds.
19. I agree for my details (which will include date of birth and NHS number or CHI number for Scotland) to be submitted to NHS Digital or other central UK NHS bodies so that information about my health may be obtained by the CTRU if necessary.
20. I understand that my GP, or any other doctor treating me, will be notified of my participation in this study.
21. I understand that some of my data may be passed to other organisations, such as the pharmaceutical companies Sanofi and Celgene, (possibly in other countries where the data protection standards and laws may be different from the UK) to monitor the safety of the treatment(s) that I am receiving. I understand that my identity will remain anonymous.
22. I agree to a copy of this Consent Form being sent to the Clinical Trials Research Unit.
23. I agree to take part in the study.

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**The following parts of the study are OPTIONAL (see section 3 of the Participant Information Sheet).** Even if you agree to take part in the RADAR study, you do not have to agree to these optional parts. Please initial yes or no.

Please initial

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A) I agree to take part in the Quality of Life and Healthcare Resource Use studies by completing questionnaires at timepoints throughout the study.

Yes No

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B) I give permission for samples that I provide to be used in future research that receives ethical approval, and I understand that this includes the bone marrow samples provided at the time of my diagnosis (if I consented separately to collection of the diagnostic bone marrow sample in anticipation of participation in this study). I understand that my samples and data collected from them may be shared on a collaborative basis with researchers in the UK and, potentially, centres abroad.

Yes No

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

Date.....

(If used) Translator:

Signature.....

Name (block capitals).....

Date.....

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

For peer review only



**Part B: Randomisation 1 Treatment Group**

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)**  
**INFORMED CONSENT DOCUMENT PART B**  
**R1 Treatment Group**

PLEASE INITIAL  
EACH BOX

24.I confirm that I have read and understand the Part B information document for the RADAR study and have had the opportunity to ask questions.

25.I agree to continue my participation in the study as part of the R1 Treatment Group.

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

Date.....

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For peer review only

**Part C: Randomisation 2 Treatment Group**

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)  
INFORMED CONSENT DOCUMENT PART C  
R2 Treatment Group**

**PLEASE INITIAL  
EACH BOX**

26.I confirm that I have read and understand the Part C information sheet for the RADAR study and have had the opportunity to ask questions.

27.I agree to continue my participation in the study as part of the R2 Treatment Group.

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

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6 (If used) Translator:  
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10 Name (block capitals).....  
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For peer review only

**Part D: Randomisation 3 Treatment Group**

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)  
INFORMED CONSENT DOCUMENT PART D  
R3 Treatment Group**

**PLEASE INITIAL  
EACH BOX**

28. I confirm that I have read and understand the Part D information sheet for the RADAR study and have had the opportunity to ask questions.

29. I agree to continue my participation in the study as part of the R3 Treatment Group.

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

Date.....

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## 8 Central Sample Analysis

The trial has 3 central laboratories receiving samples for trial purposes. The time points and the reason for analysis for each central sample can be found in Figure 2. Details on the analysis of each sample is below. Note that participants can consent for their samples to be used in future research and hence each laboratory can store their trial samples for use in future studies. The storage details are also included below.

### Birmingham

The Birmingham University Clinical Immunology Laboratory holds UKAS ISO 15189:2012 - Medical Laboratories accreditation. The Trial-related Laboratory Work will be performed using standard assays to the same quality standard as during routine clinical care. The Laboratory will be responsible for the analysis of whole clotted blood, serum and urine collected from participants of the Research Project in accordance with the Protocol. The laboratory will measure disease response and Disease progression, defined according to the IMWG 2016 response criteria for Multiple Myeloma<sup>21 26-28</sup>. This will include assessment of prognostic markers, markers of disease activity and M-protein levels. Analyses will include serum levels of beta-2 microglobulin, immunoglobulins IgG, IgA and IgM, kappa and lambda free immunoglobulin light chains. Serum electrophoresis and immunofixation, M-protein quantitation including total protein and densitometry. Urine immunofixation and free light chain quantitation will be performed where appropriate. As the trial proceeds new biomarkers of myeloma disease activity are likely to become available and will also be measured. The Laboratory will ensure that the Materials are received, handled, analysed, stored and destroyed in line with the individual consent provided.

### HMDS

The presence of minimal residual disease will be assessed in bone marrow aspirates using a validated flow cytometry assay (sensitivity  $\leq 0.001\%$ ) performed at a single central laboratory (HMDS, Leeds Teaching Hospitals Trust). A minimum of 2,500,000 cells will be evaluated with an eight-colour antibody combination of CD138, CD38, CD45, CD19, CD56, CD27, CD81 and CD117. Additional antigens for detection of CD38-negative plasma cells will be utilised as required. % neoplastic plasma cells and % normal plasma cells as a percentage of leucocytes will be reported. Limit of detection (LoD) and limit of quantification (LoQ) will also be calculated for each sample. Samples will be used for trial purposes only and will not be stored for future research.

## UCL

### **Bone marrow aspirates, peripheral blood and bone marrow trephine processing within UCL Myeloma Lab for RADAR clinical trial**

#### **OBJECTIVES**

To provide molecular and genetic data on bone marrow immune profiles of newly diagnosed myeloma patients prior and post autologous stem cell transplantation. This will also be analysed between study arms to compare how different treatment regimes alert immune landscape in patients in particular anti-CD38 mAb Isatuximab.

#### **METHODS**

##### **BMA and PB:**

1. Sites are requested to collect samples and ship as per Lab Manual together with completed sample request form.
2. All samples will be processed in Myeloma Lab at UCL Cancer Institute.
3. UCL ECMC GCLP Facility will serve as storage facility for the following materials: PB plasma, BM serum, pellets (BM, PB, CD138+ and CD138-), protein lysates, extracted RNA and DNA. All material to be stored at -80°C.
4. Myeloma Lab will serve as processing facility for all samples and storing of the following materials: BM MNCs (mononuclear cells), PB MNCs, CD138+ cells and CD138- cells. All material to be stored in liquid nitrogen.
5. Both -80°C freezers and liquid nitrogen tanks are temperature monitored with systems that alert when temperature is out of acceptable range.
6. All samples and material extracted will be logged into the trial specific lab book and database with a unique trial ID, lab ID and time-point.
7. Upon arrival bone marrow aspirates and peripheral blood will be centrifuged. Serum (from BMA) and plasma (from PB) will be collected, aliquoted into 1-1.5ml aliquots and frozen at -80°C.
8. BMA and PB mononuclear cells will then be isolated and enriched using Ficoll density gradient centrifugation.
9. PB MNCs will then be frozen as pellets and/or cryopreserved.
10. Depending on the tumour burden in the BM MNCs samples will be either frozen as MNCs pellets and/or cryopreserved or tumour cells will be isolated.



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- 3 11. Tumour will be isolated via column-based MACS cell positive selection using CD138 magnetic
- 4 beads (MicroBeads).
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- 7 12. Depending on the number of cells isolated, CD138+ plasma cells will be frozen and stored as
- 8 pellets and/or protein lysates and/or cryopreserved.
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- 10
- 11 13. CD138- cells will be frozen and stored as pellets and/or cryopreserved.
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#### Bone marrow trephine:

- 15
- 16 1. Sites are requested to collect, process and ship samples as per Lab Manual together with
- 17 completed sample request form.
- 18
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- 20 2. Myeloma lab will serve as storage facility for bone marrow trephine slides.
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- 23 3. Upon arrival all samples will be logged into trial specific database with a unique trial ID, lab
- 24 ID and time-point.
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- 26 4. Upon arrival slides will be labelled and stored in the air-tight slide storage box.
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#### ANALYSIS

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- 34 1. High-dimensional flow cytometry will be used to profile immune context of patient bone
- 35 marrow mononuclear cells prior and post-transplant.
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- 37 2. Selected samples will be analysed further using transcriptomic profiling, T cell receptor (TCR)
- 38 sequencing or single cell sequencing and multiplex
- 39 immunofluorescence/immunohistochemistry on bone marrow trephine biopsies.
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# BMJ Open

## Risk and response adapted therapy following autologous stem cell transplant in patients with newly diagnosed multiple myeloma (RADAR (UK-MRA Myeloma XV Trial): study protocol for a Phase II/III randomised controlled trial

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	Asher, Samir; UCL Cancer Institute Yong, Kwee; UCL Cancer Institute
<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Haematology (incl blood transfusion)
Keywords:	Myeloma < ONCOLOGY, Myeloma < HAEMATOLOGY, Clinical trials < THERAPEUTICS, Cancer genetics < GENETICS, STATISTICS & RESEARCH METHODS, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT



# Risk and response adapted therapy following autologous stem cell transplant in patients with newly diagnosed multiple myeloma (RADAR (UK-MRA Myeloma XV Trial): study protocol for a Phase II/III randomised controlled trial

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Word count: 8343

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## **Abstract**

### **Introduction**

Multiple myeloma is a plasma cell malignancy that accounts for 1-2% of newly diagnosed cancers. At diagnosis, approximately 20% of patients can be identified, using cytogenetics, to have inferior survival (high-risk). Additionally, standard-risk patients, with detectable disease (minimal residual disease (MRD)-positive) post-autologous stem cell transplant (ASCT), fare worse compared to those who do not (MRD-negative). Research is required to determine whether a risk-adapted approach post-ASCT could further improve patient outcomes.

### **Methods**

RADAR is a UK, multi-centre, risk-adapted, response-guided, open-label, randomised controlled trial for transplant-eligible newly diagnosed multiple myeloma patients, using combinations of lenalidomide (R), cyclophosphamide (Cy), bortezomib (Bor), dexamethasone (D) and isatuximab (Isa).

Participants receive RCyBorD(x4) induction therapy, followed by high-dose melphalan and ASCT. Post-ASCT, there are three pathways.

1. A phase III discontinuation design to assess de-escalating therapy in standard-risk MRD-negative patients. Participants receive 12 cycles of Isa maintenance. Those who remain MRD-negative are randomised to either continue or stop treatment.
2. A phase II/III multi-arm multi-stage design to test treatment strategies for treatment escalation in standard-risk MRD-positive patients. Participants are randomised to either; R, RBorD(x4) +R, RIsa, or RBorIsaD(x4) + RIsa.
3. A phase II design to assess the activity of intensive treatment strategies in high-risk patients. Participants are randomised to RBorD(x4) +R or RBorIsaD(x4) + RIsa.

1400 participants will be registered to allow for 500, 450 and 172 participants in each pathway. Randomisations are equal and treatment is given until disease progression or intolerance.

### **Ethics and dissemination**

Ethical approval was granted by the London–Central Research Ethics Committee (20/LO/0238) and capacity and capability confirmed by the appropriate local research and development department for each participating centre prior to opening recruitment. Participant informed consent is required before trial registration and re-confirmed post-ASCT. Results will be disseminated by conference presentations and peer-reviewed publications.

### **Trial registration**

ISCRTN 46841867

**Key Words: Newly Diagnosed, Multiple Myeloma, Transplant-eligible, Risk-adapted, Treatment escalation, Treatment de-escalation**

## Article Summary

### Strengths and limitations of the study

#### Strengths

- RADAR trial treatment is personalised through the utilisation of baseline cytogenetic and dynamic MRD-based stratification within its design which includes a de-escalation strategy to determine whether patients responding to treatment need to continue treatment until progression.
- RADAR is adaptive, new experimental treatment arms are expected to be added as new evidence emerges.

#### Limitations

- Patients achieving <PR to induction therapy will not proceed with on-study ASCT and will be treated off-trial, there is no trial pathway for these participants.
- RADAR excludes patients with impaired renal impairment (defined as CrCl <30 ml/min)



## **Introduction**

### **Multiple Myeloma**

Multiple myeloma (MM) is the second most common haematological malignancy with over 5500 patients diagnosed in the UK each year.[1] Whilst there is no established cure, survival has extended markedly in the last 15 years such that patients diagnosed today can expect to live a median of 6 years, and 30% will live for 10 years or longer.[1, 2]

These advances have been made possible due to the now standard use of “novel agents” including proteasome inhibitors and immunomodulatory agents (IMiD® agents) in conjunction with high-dose melphalan (HDM) supported by autologous stem cell transplantation (ASCT). Whilst MM is predominantly a disease of older people, around 40% of patients are young and fit enough at diagnosis to be eligible for ASCT, a strategy shown in several randomised trials (RCT) to extend progression-free survival (PFS).[2-4]

Improved response rates and increased survival poses challenges for the evaluation of new regimens in a timely manner. Recent studies re-evaluating the role of ASCT in the era of novel agents have confirmed superior PFS in patients allocated to ASCT compared to those allocated to chemotherapy with deferred ASCT.[5] No overall survival (OS) benefit has been seen yet, although this probably reflects the frequent use of salvage ASCT at second remission in most trial patients. Such studies utilise post-ASCT continuous therapy (lenalidomide maintenance) [6] that can extend PFS and OS,[7] but may also impact on quality of life (partly due to treatment-related toxicity), and are not without long-term risk.[8] It is thus imperative to identify those patients who are likely to benefit from extended maintenance therapy, in order to reduce health care costs and minimise toxicity for those who do not benefit.

### **Existing Evidence: Induction Therapy**

Treatment with lenalidomide (R), cyclophosphamide (Cy), bortezomib (Bor) and dexamethasone (D) (RCyBorD) was studied as first line therapy in the Phase 2 EVOLUTION study, where it produced high response rates and deep responses compared to CyBorD or LenBorD.[9]

### **Existing Evidence: High-Risk Patients**

At diagnosis, a small subgroup of patients (approximately 20%) can be identified on the basis of genetic features to have inferior survival regardless of treatment regimen (high-risk patients).[10-12] For such patients, and for those patients with refractory disease (no response to first line therapy), outcomes have remained poor despite the introduction of novel agents[13-15]. Whilst high-risk patients often show a good response to induction therapy, the durability of the response is inferior to standard-risk patients. Using the R-ISS which incorporates high risk cytogenetic features into the the International Staging System (ISS), PFS time is 66 months for R-ISS stage I, 42 months for R-ISS stage II, and 29 months for R-ISS stage III)[16]. The attainment of MRD-negative disease is also critical.[17-19] The activity of the RBorD regimen in patients with high-risk disease looks promising[20], and there is a question of whether an additional benefit may be gained through the use of anti-CD38 immunotherapy. Anti-CD38[21, 22] antibodies have single agent activity, but also impressive efficacy in combination, particularly with IMiD agents, lenalidomide and pomalidomide. In the RADAR trial the anti-CD38 antibody isatuximab (Isa) (SAR650984) will be used. Isatuximab is a naked immunoglobulin

(Ig) G1 derived monoclonal antibody (mAb) that binds selectively to a unique epitope on the human surface antigen called CD38 [23].

### **Existing Evidence: Standard-Risk Patients**

With increasingly effective multi-drug regimens being used for induction treatment, and responses further deepened following high-dose therapy and ASCT, the major challenge for standard-risk participants is how to maintain their disease control for as long as possible. The benefit of post-ASCT consolidation approaches remains controversial, with inconsistent evidence identifying both appropriate patient groups and treatment strategies.

Maintenance lenalidomide (R) has been studied within several large studies and has consistently been shown to increase PFS, confirmed within a recent meta-analysis.[7] The impact of long-term lenalidomide therapy on bone marrow and immune function, and general wellbeing are not completely understood. Thus there is an urgent need to identify those patients who benefit most from this approach, as well as an evaluation of other agents that utilise the host immune system to improve outcomes, such as antibodies. It is also of benefit to explore the option and effect of stopping maintenance therapy in patients who have achieved and maintained the deepest response

### **Existing Evidence: Use of MRD for stratifying treatment in standard-risk patients**

MRD status is a clinically relevant biomarker, and an emerging clinical trial endpoint with recent guidance published by the International Myeloma Working Group (IMWG).[19, 24]

Several studies have shown that patients who have detectable disease in their bone marrow (MRD-positive) following ASCT suffer earlier relapses and shorter survival when compared with those who are MRD-negative.[25, 26] These results have been combined in a recent meta-analysis.[26] Hence these patients should be the focus of investigative strategies aimed at deepening disease response and converting them from MRD-positive to MRD-negative.

Patients without detectable disease in their bone marrow (MRD-negative), have longer PFS and OS.[27] In the IFM2009 study that randomised patients to receive ASCT upfront or to continue chemotherapy, patients who were MRD-negative fared equally well, regardless of whether they had received ASCT, or chemotherapy alone. This would suggest that those who have achieved MRD-negative response may not need to undergo intensive consolidation therapy, and instead may benefit from a de-escalation of therapy.

### **Aims and objectives**

RADAR aims to address the most important contemporary therapeutic questions for newly diagnosed multiple myeloma transplant eligible (NDMM TE) patients post-ASCT by considering three different post-ASCT treatment pathways:

1. A de-escalation treatment strategy is used to determine whether ceasing Isa maintenance treatment, after 12 cycles of continuous treatment, is non-inferior to long-term Isa treatment, in terms of progression-free survival (PFS) in participants who are standard-risk at diagnosis (participants who have  $\leq 1$  high-risk cytogenetic lesion) and are MRD-negative at 100 days post-ASCT and 12 months (cycles) after.

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2. A treatment escalation strategy is used for participants who are standard-risk at diagnosis (participants who have  $\leq 1$  high-risk cytogenetic lesion) and MRD-positive at 100 days post ASCT. The trial aims to compare the activity and efficacy of post-ASCT consolidation and maintenance treatment between combinations of R, Bor, D and Isa to R alone in terms of conversion to MRD-negativity.
3. Dose-intensive consolidation and maintenance strategies will be studied for participants who are high-risk at diagnosis (participants who have  $> 1$  high-risk cytogenetic lesion). The activity of post-ASCT strategies containing R, Bor, D and Isa will be assessed in terms of PFS rate.

## Trial Design

RADAR is a national, multi-centre, risk-adapted, response-guided open-label, randomised controlled trial for NDMM TE patients: phase II/III for standard-risk, MRD-Positive participants, phase III randomised discontinuation design for standard-risk, MRD-Negative participants, phase II randomised for high-risk participants. The following report details the trial protocol and follows the structure of the SPIRIT statement.[28] The SPIRIT checklist can be found within the supplementary material.

## Methods:

### Setting

The RADAR trial will be conducted at 70 centres in the United Kingdom (See supplementary material), as identified via a feasibility assessment to determine those most appropriate to participate in the trial.

Potential participants will be identified by the research team at the time they are referred to the haematology outpatient department with suspected multiple myeloma. A smaller number of participants may be identified during inpatient admissions. Invitation to participate in the trial and provision of information will be made either during their first consultation, when routine diagnostic tests will be performed and potential treatment options discussed, or at the time they receive their diagnostic test results.

### Eligibility criteria

Adults (18 years and older) with previously untreated multiple myeloma requiring therapy, as defined by IMWG diagnostic criteria, who are eligible for stem cell transplant and capable of giving informed consent will be assessed for eligibility. Eligibility will be confirmed prior to; registration, the start of isatuximab maintenance treatment in the Randomisation 1 pathway and each randomisation by the principal investigator (PI) or an appropriately authorised medically trained delegate and will be recorded in the participants' medical records and on the relevant electronic case report form (eCRF).

To be eligible for each point in the trial the participants must meet all the inclusion criteria and none of the exclusion criteria presented in Table 1 for trial registration, Table 2 for isatuximab treatment in the R1 pathway, Table 3 for Randomisation 1 (R1), Table 4 for Randomisation 2 (R2), Table 5 for Randomisation 3 (R3).

Table 1: Inclusion and Exclusion Criteria for Main Trial Registration

<b>Inclusion Criteria:</b>	
1.	Previously untreated patients with multiple myeloma requiring therapy, defined as having myeloma defining events or with biomarkers of malignancy according to IMWG diagnostic criteria
2.	Eligible for stem cell transplant
3.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression);
4.	Total bilirubin $\leq 1.5$ x upper limit of normal (ULN)
5.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3$ x ULN (if ALT <b>and</b> AST are tested, both must meet this criteria)
6.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/L</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/L</math> is allowed),</li> <li>• haemoglobin (Hb) <math>\geq 80g/L</math>. Blood transfusions within 3 days prior to eligibility assessments are <b>not permitted</b>,</li> <li>• platelets <math>\geq 75 \times 10^9/L</math> (in the case of heavy bone marrow infiltration (&gt;50%) which is, in the opinion of the investigator, the cause of the thrombocytopenia and provided appropriate supportive measures and patient monitoring are in place, a platelet count of <math>\geq 50 \times 10^9/L</math> is permitted. Platelet transfusions within 3 days prior to eligibility assessments are <b>not permitted</b>.</li> </ul>
7.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
8.	Able to swallow oral medication
9.	Aged at least 18 years
10.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ol style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest, OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ol style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Contraception for female and male participants must be in accordance with (and participants must consent to) the Celgene Pregnancy Prevention Plan.</p> <p>If female and of childbearing potential, they must have a negative pregnancy test performed by a healthcare professional within 14 days prior to registration.</p>
11.	Able to provide written informed consent.
<b>Exclusion Criteria</b>	
1.	Asymptomatic (smouldering) MM, monoclonal gammopathy of undetermined significance (MGUS), solitary plasmacytoma of bone, or extramedullary plasmacytoma (without evidence of MM)

2. Received previous treatment for MM, with the exception of local radiotherapy to relieve bone pain or spinal cord compression, prior bisphosphonate treatment, or corticosteroids as long as the total dose does not exceed the equivalent of 160mg dexamethasone. *This criteria is not applicable at R1, R2 and R3 when participants will have received previous treatment for MM as part of this trial.*
3. Unstable angina or myocardial infarction within 4 months prior to registration (or at any time since registration for participants starting isatuximab maintenance, R1, R2 and R3), NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
4. Cardiac disorder identified according to local practice (eg left ventricular ejection fraction, LVEF; results from formal measurements acceptable within 28 days prior to registration)
5. Significant neuropathy (Grade  $\geq 3$ , or Grade 2 with pain)
6. Prior malignancy that required treatment or has shown evidence of recurrence (except for non-melanoma skin cancer or adequately treated cervical carcinoma in situ) during the 5 years prior to registration. Cancer treated with curative intent for >5 years previously and without evidence of recurrence will be allowed.
7. Pregnant, lactating or breastfeeding female participants
8. Known resistance, intolerance or hypersensitivity to any component of the planned therapies, except in the case of hypersensitivity which is amenable to premedication with steroids or H2 blocker. Intolerance includes hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption.
9. Major surgery within 14 days before registration (or starting isatuximab maintenance, R1, R2 and R3). This would include surgical intervention for relief of cord compression but does not include vertebroplasty or kyphoplasty.
10. Known gastrointestinal (GI) disease or GI procedure that could interfere with the oral absorption or tolerance of trial treatment, including difficulty swallowing.
11. Active systemic infection
12. Participant is hepatitis B surface antigen positive, hepatitis C antibody positive or HIV positive (participants who are hepatitis C core antibody positive but have been successfully treated for the disease may still be eligible – please consult the CTRU/CI). Participants must have hepatitis and HIV screening conducted within 28 days prior to registration.
13. Any other medical or psychiatric condition which, in the opinion of the investigator, contraindicates the participant's participation in this study.
14. Receipt of live vaccination within 30 days prior to registration, for the duration of the study and for 3 months after the last dose of study drug.
15. Participant has risk factors for thromboembolism including the use of agents which may increase their risk of thrombosis, such as hormone replacement therapy (*this exclusion criteria is applicable only at registration and when starting R2 or R3 pathway*)
16. Participant has risk factors for seizures (*this exclusion criteria is applicable only at registration and when starting R2 or R3 pathway*)

Table 2: Inclusion and Exclusion criteria for Isatuximab treatment (R1 Pathway)

<b>Inclusion Criteria:</b>	
<ol style="list-style-type: none"> <li>1. Standard-risk (participant is not <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q), as confirmed by the CTRU.</li> <li>2. 4 cycles of RCyBorD received</li> <li>3. MRD-negative (proportion of malignant cells in the bone marrow is &lt; 1 in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT</li> <li>4. Received <math>\geq 100\text{mg}/\text{m}^2</math> high-dose melphalan and ASCT</li> <li>5. Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG &gt;2 is due to effects of myeloma eg spinal cord compression)</li> <li>6. Total bilirubin <math>\leq 1.5 \times</math> upper limit of normal (ULN )</li> <li>7. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) <math>\leq 3 \times</math> ULN (if ALT <b>and</b> AST are tested, both must meet this criteria)</li> <li>8. Adequate marrow function:               <ol style="list-style-type: none"> <li>a) neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>b) Hb <math>\geq 80\text{g}/\text{L}</math>. Blood transfusions within 3 days prior to eligibility assessments are not permitted,</li> <li>c) platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> </ol> </li> <li>9. Creatinine clearance (CrCl) <math>\geq 30</math> mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)</li> <li>10. Agree to follow the pregnancy prevention guidelines:               <p>Female participants who:</p> <ol style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ol style="list-style-type: none"> <li>e) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest OR</li> <li>f) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or until 5 months after the last dose of study drug, whichever is longest.. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>g) Agree to not donate sperm during the entire study treatment period until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ol> </li> <li>11. Signed the Informed Consent Document for the R1 treatment pathway.               <ol style="list-style-type: none"> <li>a)</li> </ol> </li> </ol>	
<b>Exclusion Criteria:</b>	
<ol style="list-style-type: none"> <li>1. Disease progression (according to IMWG criteria)</li> <li>2. MRD-positive (proportion of malignant cells in the bone marrow is <math>\geq 1</math> in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT</li> <li>3. Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)</li> </ol>	

Table 3: Inclusion and Exclusion criteria for Randomisation 1

<b>Inclusion Criteria:</b>	
1.	Standard-risk (participant is not <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q), as confirmed by the CTRU.
2.	12 cycles of isatuximab maintenance received
3.	MRD-negative (proportion of malignant cells in the bone marrow is < 1 in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT
4.	MRD-negative (proportion of malignant cells in the bone marrow is < 1 in 100,000, confirmed by HMDS central lab) after 12 cycles of isatuximab
5.	Received $\geq 100\text{mg/m}^2$ high-dose melphalan and ASCT
6.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression)
7.	Total bilirubin $\leq 1.5 \times$ upper limit of normal (ULN)
8.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3 \times$ ULN (if ALT and AST are tested, both must meet this criteria)
9.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>• Hb <math>\geq 80\text{g/L}</math>. Blood transfusions within 3 days prior to eligibility assessments are not permitted,</li> <li>• platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> </ul>
10.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
11.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ul style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 5 months after the last dose of study drug, OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject from the time of signing the informed consent form until 5 months after the last dose of study drug. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 5 months after the last dose of study drug.</li> </ul> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ul style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 5 months after the last dose of study drug, OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 5 months after the last dose of study drug. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until 5 months after the last dose of study drug.</li> </ul>
12.	Signed the Informed Consent Document for the R1 treatment pathway.
<b>Exclusion Criteria</b>	
1.	Disease progression (according to IMWG criteria)
2.	MRD-positive (proportion of malignant cells in the bone marrow is $\geq 1$ in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT or after 12 cycles of isatuximab
3.	Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)

Table 4: Inclusion and Exclusion Criteria for Randomisation 2

<b>Inclusion Criteria:</b>	
1.	Standard-risk (participant is not <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q) as confirmed by CTRU.
2.	4 cycles of RCyBorD received
3.	MRD-positive (proportion of malignant cells in the bone marrow is $\geq 1$ in 100,000, confirmed by HMDS central lab) at 100 days post-ASCT
4.	Received $\geq 100\text{mg}/\text{m}^2$ high-dose melphalan and ASCT
5.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression)
6.	Total bilirubin $\leq 1.5$ x upper limit of normal (ULN )
7.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3$ x ULN (if ALT and AST are tested, both must meet this criteria)
8.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>• Hb <math>\geq 80\text{g}/\text{L}</math></li> <li>• platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> </ul>
9.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
10.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ul style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ul style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul>
11.	Signed the Informed Consent Document for the R2 treatment pathway.
<b>Exclusion Criteria:</b>	
1.	Disease progression (according to IMWG criteria)
2.	Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)



Table 5: Inclusion and Exclusion criteria for Randomisation 3

<b>Inclusion Criteria:</b>	
1.	High-risk (participant is <b>confirmed</b> to have at least two of these genetically adverse lesions: t(4;14), t(14;16), t(14;20), del(17p), gain(1q)) as confirmed by CTRU.
2.	4 cycles of RCyBord received
3.	Received $\geq 100\text{mg/m}^2$ high-dose melphalan and ASCT
4.	Eastern Cooperative Oncology Group (ECOG) performance status 0–2 (except in cases where ECOG >2 is due to effects of myeloma eg spinal cord compression)
5.	Total bilirubin $\leq 1.5$ x upper limit of normal (ULN )
6.	Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) $\leq 3$ x ULN (if ALT and AST are tested, both must meet this criteria)
7.	Adequate marrow function: <ul style="list-style-type: none"> <li>• neutrophils <math>\geq 1.0 \times 10^9/\text{L}</math> (unless the participant has a known/suspected diagnosis of familial or racial neutropenia in which case an ANC <math>\geq 0.75 \times 10^9/\text{L}</math> is allowed),</li> <li>• Hb <math>\geq 80\text{g/L}</math></li> <li>• platelets <math>\geq 75 \times 10^9/\text{L}</math>. Platelet transfusions within 3 days prior to eligibility assessments are not permitted</li> <li>• Creatinine clearance (CrCl) <math>\geq 30</math> mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)</li> </ul>
8.	Creatinine clearance (CrCl) $\geq 30$ mL/minute, according to the Cockcroft-Gault formula, following correction of reversible causes (e.g. dehydration, hypercalcaemia, sepsis)
9.	Agree to follow the pregnancy prevention guidelines: <p>Female participants who:</p> <ul style="list-style-type: none"> <li>a) Are not of childbearing potential, OR</li> <li>b) If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>c) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject from the time of signing the informed consent form until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)</li> <li>d) Agree to not donate oocytes during the entire study treatment period and until 12 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul> <p>Male participants, even if surgically sterilised (i.e. status post-vasectomy), must agree to one of the following:</p> <ul style="list-style-type: none"> <li>a) Agree to practice effective barrier contraception during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest OR</li> <li>b) Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest. (Periodic abstinence [e.g. calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception).</li> <li>c) Agree to not donate sperm during the entire study treatment period and until 6 months after the last dose of cyclophosphamide or 5 months after the last dose of study drug, whichever is longest.</li> </ul>
10.	Signed the Informed Consent Document for the R3 treatment pathway.
<b>Exclusion Criteria</b>	
1.	Disease progression (according to IMWG criteria)
2.	Registration exclusion criteria (cardiac risk assessment, HIV and Hepatitis B and C testing do not need to be repeated)

## Interventions and Dosing

### *Intervention Schedule*

All participants will receive four, 21 day, cycles of induction treatment with RCyBorD. During this time, the genetics risk status of the participant will be analysed and determined from bone marrow samples prior induction treatment (from diagnosis or trial-specific procedures). Participants will either be allocated as high risk (defined as the presence of at least 2 of these adverse lesions: t(4,14), t(14,16), t(14,20), del(17p) or gain(1q)) or standard risk. At the end of the induction cycle participants will be assessed for response. In the absence of disease progression or intolerance, participants with at least a partial response (PR) will proceed to HDM and ASCT which will be carried out according to local practice. At 100 days post-ASCT participants will be assessed for MRD and response and will follow one of three pathways of post ASCT treatment, provided they meet the eligibility criteria:

1. Participants identified as standard risk and who are MRD-negative post-ASCT will be treated according to the R1 pathway. All participants will receive 12 cycles of Isa maintenance treatment. Those who remain MRD-negative following cycle 12, will be randomised to continue or stop Isa maintenance treatment.
2. Participants identified as standard-risk and who are MRD-positive post-ASCT and have at least a minimal response (MR) at 100 days post ASCT, will proceed to R2. Eligible participants will be randomised between: R maintenance; RBorD consolidation and R maintenance (RBorD + R); RIsa maintenance; or RBorIsaD consolidation and RIsa maintenance (RBorIsaD + RIsa).
3. Participants identified as high-risk and have at least a partial response (PR) at 100 days post ASCT will proceed to R3. These participants will be randomised to receive either RBorD consolidation, followed by R maintenance; or RBorIsaD consolidation followed by RIsa maintenance.

All randomisations are balanced across the treatment arms. A computer generated minimisation programme that incorporates a random element will be used to ensure treatment groups are well balanced for the stratification factors of each randomisation (See Table 6).

Table 6: Stratification Factors

Randomisation:	Stratification factors:
1	<ul style="list-style-type: none"> <li>• Centre</li> <li>• Number of high risk lesions at trial registration (0 or 1 or unable to determine)</li> </ul>
2	<ul style="list-style-type: none"> <li>• Centre</li> <li>• Number of high risk lesions at trial registration (0 or 1 or unable to determine)</li> <li>• Response at 100 days post-ASCT (<math>&lt; VGPR</math>, <math>\geq VGPR</math>)</li> </ul>
3	<ul style="list-style-type: none"> <li>• Centre</li> <li>• Number of high risk lesions at trial registration (2, or <math>\geq 3</math>, or unable to determine)</li> <li>• Response at 100 days post-ASCT (<math>&lt; VGPR</math>, <math>\geq VGPR</math>)</li> </ul>

Table 7 summarises the starting doses for the induction treatment and each post-ASCT treatment pathway. Following ASCT all treatments will continue until disease progression or intolerance. Response will be assessed at the end of each cycle according to the IMWG 2016 response criteria[24, 29-31]. Treatment intolerance will be assessed throughout each treatment cycle, according to the national cancer institute (NCI) common terminology criteria for AE (CTCAE) Version 5. All consolidation cycles are 21 days in length, maintenance cycles are 28 days in length.

Table 7: Dosing schedule for R<sub>Cy</sub>BorD induction and each randomisation pathways

<b>Trial Registration- Induction (Each cycle = 21 days)</b>		
<b>Treatment (Route)</b>	<b>Induction – All participants (Starting Dose)</b>	<b>Days</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup>	1, 8, 15
<b>Cyclophosphamide (PO)</b>	500mg	1, 8
<b>Lenalidomide (PO)</b>	25mg	1-14
<b>Dexamethasone (PO)</b>	40mg	1, 8, 15
<b>Isatuximab Pre-Randomisation 1 (Each cycle = 28 day)</b>		
<b>Treatment (Route)</b>	<b>R1 pathway participants Only (Starting Dose)</b>	<b>Days</b>
<b>Isatuximab (IV)</b>	10mg/kg	1, 8, 15 and 22 cycle 1 then days 1 and 15 from cycle 2 onwards
<b>Randomisation 1: Isatuximab maintenance (Each Cycle = 28 days)</b>		
<b>Treatment</b>	<b>Isatuximab (Days)</b>	<b>“Stop Isatuximab” (Days)</b>
<b>Isatuximab (IV)</b>	10mg/kg (Day 1 Only)	None
<b>Randomisation 2: MRD-positive treatment escalation pathway</b>		
<b>Treatment Arm 1 (Control) : Lenalidomide (R) maintenance</b>		
<b>Treatment (Route)</b>	<b>Starting Dose (Days)</b>	
<b>Lenalidomide (PO)</b>	10mg/kg* (1-21 )	
<b>Treatment Arm 2: R<sub>Bor</sub>D consolidation + R Maintenance</b>		
<b>Treatment</b>	<b>Consolidation: Cycle 1-4 (each cycle = 21 days)</b>	<b>Maintenance (each Cycle = 28 days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)
<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA
<b>Treatment Arm 3:R<sub>Isa</sub> Maintenance</b>		
<b>Treatment</b>	<b>Maintenance (Days)</b>	
<b>Lenalidomide (PO)</b>	10mg* (Day 1-21)	
<b>Isatuximab (IV)</b>	10mg/kg (1, 8, 15 and 22 cycle 1 then days 1 and 15 from cycle 2 onwards)	
<b>Treatment Arm 4: R<sub>Bor</sub>IsaD + R<sub>Isa</sub></b>		
<b>Treatment</b>	<b>Consolidation Cycle 1-4: Each cycle = 21 days (Days)</b>	<b>Maintenance: Each cycle = 28 days (Days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)
<b>Isatuximab (IV)</b>	10mg/kg (1, 8, 15 cycle 1 then days 1 and 8 cycle 2, then days 1 and 15 cycle 3 onwards)	10mg/kg (1 and 15)
<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA
<b>Randomisation 3: High Risk Treatment Pathway</b>		
<b>Treatment Arm 1: R<sub>Bor</sub>D Consolidation and R maintenance</b>		
<b>Treatment</b>	<b>Consolidation: Cycle 1-4 (each cycle = 21 days)</b>	<b>Maintenance (each Cycle = 28 days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)

<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA
<b>Treatment Arm 2: RBorIsaD consolidation + RIsa Maintenance</b>		
<b>Treatment</b>	<b>Consolidation Cycle 1-4: Each cycle = 21 days (Days)</b>	<b>Maintenance: Each cycle = 28 days (Days)</b>
<b>Bortezomib (SC)</b>	1.3mg/m <sup>2</sup> (1, 8, 15)	NA
<b>Lenalidomide (PO)</b>	15mg* (1-14)	10mg* (1-21)
<b>Isatuximab (IV)</b>	10mg/kg (1, 8, 15 cycle 1 then days 1 and 8 cycle 2, then days 1 and 15 cycle 3 onwards)	10mg/kg (1 and 15)
<b>Dexamethasone (PO)</b>	20mg (1, 8, 15)	NA

\*or final dose administrated at the end of induction or consolidation treatment if lower

### *Intervention Adherence*

Throughout the trial R will be taken orally and swallowed whole at the same time on the scheduled days. D and Cy will be taken orally, whilst Bor will be administrated via a subcutaneous injection. Bortezomib may also be administered at home if this is in line with local policies and if appropriate procedures are in place. Isa will be given as an intravenous infusion and at a facility capable of managing hypersensitivity reactions.

To monitor adherence to the oral trial medicines, participants will complete a participant diary card which will be reviewed at each trial visit. Non-compliance will be reported to the CTRU and any unused capsules will be returned to the pharmacy.

### *Dose Modifications and Discontinuations*

With the exception of Isa, which can only be interrupted and resumed, dose modifications are permitted in the management of toxicities. Upfront dose modifications in response to liver and/or renal impairment are also permitted within the protocol. When the dose of any drug is reduced the dose cannot be re-escalated in this trial.

If one drug in a combination is stopped, treatment with the other drugs in combination can continue. Scenarios in which the participant may remain on trial following consultation with the Chief Investigator (CI) are if they: discontinue two or more drugs during combination therapy; cease treatment for more than three weeks in between any treatment cycle or are delayed in starting maintenance of consolidation beyond 120 days post-ASCT. Note that if Bor, R or D is stopped during the pre-ASCT induction treatment due to toxicity, the participant will only be able to be treated on the standard-risk-MRD-negative pathway (assuming they meet the relevant inclusion criteria).

If treatment is discontinued early, the participant will be treated off trial at the discretion of their treating clinician.

### *Concomitant medication:*

Local support care protocols, including anti-emetic schedules, tumour lysis syndrome prevention, venous thromboembolism prophylaxis and prophylactic antimicrobial therapy should be followed. The excluded concomitant medications and procedures whilst receiving trial treatment are listed in supplementary material.

1  
2  
3 Concomitant medication, disease and other malignancies will be recorded at eligibility.  
4  
5

## 6 **Outcomes:**

### 7 *Primary outcomes*

8  
9 PFS-R1 is defined as the time from R1 to the time of first documented evidence of disease progression  
10 or death from any cause. Individuals who are lost to follow-up or progression-free at the time of  
11 analysis will be censored at their last known date to be alive and progression-free.  
12  
13

14 Attainment of MRD-negativity is defined as a binary endpoint. MRD-negativity will be determined at  
15 6 months post-R2 (end of cycle 6 post-ASCT treatment for participants allocated to maintenance only  
16 strategies and end of cycle 7 post-ASCT treatment for participants allocated to maintenance and  
17 consolidation strategies) according to the IMWG 2016 response criteria.  
18  
19

20 The PFS rate is defined as the proportion of participants who are alive and progression-free 28 months  
21 post-R3.  
22  
23

24 Disease progression is defined according to the IMWG 2016 response criteria for Multiple Myeloma  
25 [24, 29-31].  
26

### 27 *Secondary outcomes:*

28 The secondary outcomes of this trial are to assess; PFS for R2 and R3, Time to progression, Time to  
29 second PFS event (PFS2), Overall survival (OS), Survival after progression, Objective response rate  
30 (ORR), Attainment of Very Good Partial Response ( $\geq$  VGPR), Attainment of MRD negativity, Duration  
31 of MRD Negativity, Time to improved response, Time to next treatment, Treatment compliance and  
32 total amount of therapy delivered, Toxicity and Safety, including the incidence of second malignancies,  
33 Quality of life (QoL) including EORTC-QLQ-C30, EORTC-QLQ-MY20 and EQ-5D-3L and Cost  
34 effectiveness.  
35  
36  
37  
38

### 39 *Exploratory and subgroup analyses*

40 An overview of the planned exploratory and subgroup analysis can be found in the supplementary  
41 material. These include genetic and molecular analysis of participant samples conducted by the  
42 respective central laboratories, as well as additional analysis to review the infection and re-infection  
43 rates of covid-19 in participants during induction, post-ASCT and during post ASCT consolidation.  
44  
45  
46

## 47 **Participant's timelines**

48 The full trial schema can be seen in Figure 1. The schedule of assessments at each time point are  
49 presented in Figure 2.  
50  
51

### 52 *Trial Entry*

53 Participants will enter into the trial at one of two points in their pathway, this will either be at bone  
54 marrow registration or at main trial registration.  
55  
56  
57  
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59  
60

### *Trial Consent*

Participants who enter the trial at bone marrow registration will provide consent to have bone marrow samples taken and sent to central laboratories for analysis. If the participant does not have myeloma or decides to not take part in RADAR, they will have the option of consenting to their samples being used in future research.

All participants will be required to provide written informed consent for the trial prior to trial registration (for initial trial treatment and further trial information) and prior to starting their post-ASCT treatment pathway once their post-ASCT assessments have been completed (for their pathway specific treatment). Optional consent regarding QoL and healthcare resource use questionnaires and the use of samples for future research will also be obtained within the first consent process.

Consent forms are included in supplementary material.

### *Trial Registration*

Following initial consent, participant eligibility for trial registration will be assessed. Trial samples for blood and urine will be taken for all participants and bone marrow samples will be taken for those who did not enter the trial through bone marrow registration.

### **Genetic Risk**

Bone marrow samples from diagnosis will be analysed at time of diagnosis at local cytogenetics laboratories for FISH-defined high-risk makers. Original/copy of the FISH testing report will also be sent to CTRU where they will be reviewed by the CI/Trial management team for risk stratification. Participants will either be categorised high-risk (defined as the presence of at least 2 of the following adverse lesions: t(4;14), t(4;16), t(14;20), del(17p) or gain(1q)) or standard-risk.

Participants will commence RCyBorD treatment once a diagnosis of symptomatic myeloma has been confirmed by the treating physician, and ideally when it is known that the FISH testing has been successful.

Where risk status can be determined from the first sample participants can continue on the trial. If status cannot be confirmed and the FISH report shows a full test failure i.e. no information relating to adverse lesions is available, a second attempt will be made to collect a bone marrow sample prior to treatment starting. If partial results are obtained from the FISH sample, it may be possible that the CI/trial management group (TMG) will be able to determine risk status using the assumption that translocations are mutually exclusive and that some markers are rare. If risk status can be determined a second bone marrow sample is not required. However, this must be confirmed by the CTRU.

If, after two bone marrow samples, the FISH results for some or all the adverse lesions are inconclusive participants risk will be determined using a combination of the results from the two samples. The most appropriate pathway will be determined by the CI. Note this may result in the participants stratification factor being 'unable to determine' at randomisation. If a second bone marrow has been requested by CTRU but the collection was not attempted, the participants will be taken off the study (after ASCT, if induction treatment was already started)

### *Induction and ASCT*

Following trial registration, once all central samples have been taken and risk status confirmed, participants will receive induction treatment as described in the intervention section. In the absence of disease progression or treatment intolerance participants with at least a partial response (PR) to will proceed to HDM and ASCT.

Consenting participants will complete QoL and resource use questionnaires at the end of RCyBorD induction treatment.

All participants who go through ASCT will have a bone marrow sample taken at 100 days (+/- 14) post-ASCT. If an MRD result cannot be obtained at the first attempt, the bone marrow will be repeated once (within 28 days after 100 days post-ASCT time point). If the second attempt fails, the participant will be considered MRD-positive.

### *Post-ASCT Treatment*

Participants who receive all 4 cycles of induction treatment followed by ASCT will be assessed for eligibility into their assigned randomisation pathways determined by genetic risk and MRD results and treated as described in the intervention schedule.

Consenting participants in the R1 pathway will complete QoL and resource use questionnaires after cycle 6, 12, 24 and 36 (participants randomised to "stop Isa" will complete the cycle 24 and 36 QoL and resource use questionnaires at equivalent time points).

Similarly, consenting participants to receive R or RI<sub>sa</sub> within pathway R2 and R3 will complete QoL and resource use questionnaires after cycles 6, 12 and 24 of maintenance. Those randomised to receive RBorI<sub>sa</sub>+R or RBorI<sub>sa</sub>D+RI<sub>sa</sub> will complete QoL and resource use questionnaires after cycles 3, 9 and 21 of maintenance.

Post-ASCT treatment (including observation only in the R1 pathway) is continued until disease progression, participant or clinician withdrawal or death. After treatment discontinuation, the participant is treated off trial by their local clinician and followed-up as per the trial follow-up schedule.

### *Trial Follow-up*

Participants who discontinue during induction and until 100 days post-ASCT will be followed up for data pertaining to safety, details of salvage treatment, progression (including second progression), and survival at standard care visits. Follow ups will be conducted every 2 months up until disease progression, death or the end of trial. Similar follow-up will be completed for participants who discontinue their allocated trial treatment, which started post-ASCT. In addition consenting participants will still complete QoL and resource use questionnaires at appropriate time points.

All types of adverse event/reaction will be collected until 60 days after the last dose of protocol treatment.

1  
2  
3 Following disease progression all participants will be followed up annually until death, or until the end  
4 of the trial.  
5  
6

### 7 **Sample size**

8  
9 In total 1400 participants will be recruited into the trial. Accounting for participants who will be lost  
10 to follow-up, this allows for 500, 450 and 172 participants to enter each randomisation, respectively.  
11  
12

#### 13 *Randomisation 1*

14 Data from our previous trial Myeloma XI, suggests that approximately 50 participants will lose their  
15 MRD-negative status during the first 12 cycles of Isa maintenance. In addition, Myeloma XI estimated  
16 median PFS with continuous R to be 50 months amongst TE participants.[32] Under these assumptions  
17 and allowing for our randomisation being 12 months later, 500 participants allows for 80% power to  
18 test a non-inferiority margin of 10% at 2 years post-R1 (this equates to a hazard ratio of 1.38) with a  
19 one-sided 5% significance level, allowing for approximately 20% further drop-out after R1 amongst  
20 participants unwilling to cease treatment or being lost to follow-up.  
21  
22  
23

24  
25 A power of 80% will be attained when 238 PFS events have been observed. These calculations assume  
26 that PFS follow an exponential distribution and that there will be 3 years of recruitment to R1 and 2  
27 further years of follow-up (in order that all participants can have PFS at 2 years post-R1 assessed).  
28  
29

30 Global Health Status/Quality of Life is considered a key secondary endpoint of R1 as the conclusion  
31 that the cessation of continuous treatment is non-inferior should not come at the expense of quality  
32 of life. Ignoring those required to account for participants lost to follow-up, the 406 participants  
33 recruited above give >95% power to detect a difference of 10 points at 2 years post-R1, where 10  
34 points represents an accepted medium magnitude clinically relevant difference.[33] The calculation  
35 uses data collected from the intensive pathway of MRC Myeloma IX to estimate that the standard  
36 deviation in the Global Health Status/QoL subscale of EORTC-QLQ-C30 as 27.54 along with a two-sided  
37 5% significance level.[34]  
38  
39  
40  
41  
42

#### 43 *Randomisation 2*

44 R2 is a multi-arm, multi-stage drug/drug-combination assessment platform with seamless phase II  
45 (activity) and phase III (efficacy) stages. Each experimental arm is compared with a designated control  
46 arm (R maintenance).  
47  
48

49 Early data from Myeloma XI and similar data from IFM/DFCI 2009 [35] suggest that a 10% upgrade in  
50 MRD-negative rate after 6 months continuous R treatment is achievable. It is thought that RBoRD  
51 consolidation followed by attenuated continuous R or continuous R combined with antibody or  
52 immunotherapy could lead to a 30% increase in MRD-negative rate, a 20% upgrade of increase at 6  
53 months post-randomisation when compared to continuous R treatment, as good as therapy  
54 combinations containing an alternative proteasome inhibitor.<sup>33</sup>  
55  
56  
57

58 Following the strategy of Bratton and colleagues [36] for a multi-arm multi-stage trial with:

- 59 • N=2 stages (Stage 1 (activity) and Stage 2 (efficacy)) and  
60



- J=4 experimental arms (R<sub>BorD</sub>+R, R+I<sub>sa</sub>, R<sub>BorI<sub>sa</sub>D</sub> + I<sub>sa</sub> and TBC) and a single control arm (R)
- Where allocation is equal across each arms (1:1:1:1:1) and
- The power in Stage 1 and Stage 2 is 95% and 85%, respectively,
- the one-sided significance level in Stage 1 and Stage 2 is 25% and 1%, respectively,
- 10 participants per month are entered at R<sub>2</sub>, Stage 1 (activity) analysis and reporting requires 1 month and 5% of participants drop-out.

This equates to 40 participants in each arm at Stage 1 and 50 further participants in each arm at Stage 2. This will require a maximum of 46 months of recruitment plus a further 6 months of follow-up for the final participant. Overall, this design has a power of 83.4% and a one-sided family-wise error rate (FWER) of ~3%.

Randomisation 2 has been powered assuming four experimental arms and that all experimental arms will continue to stage 2. In the case that only three experimental arms are implemented or at least one experimental arm is concluded to show a lack of activity after stage 1, the trial will have a higher power than stated above.

### *Randomisation 3*

Each arm of R<sub>3</sub> will take the form of one-stage treatment design proposed by Simon, Wittes and Ellenberg [37] where the A'Hern design [38] is first implemented to determine treatment activity in both arms. Treatment activity will be determined by considering the PFS rate at 28 months. Data from Myeloma XI demonstrated a median PFS for high-risk participants in the intensive pathway of approximately 19 months (unpublished data). It is thought that for the treatments proposed to be investigated further in a Phase III trial they should increase the median PFS from 19 months to at least 28 months (9 month increase), i.e. increasing the PFS rate at 28 months from 34.7% to 50%.

In order to have an 80% power of demonstrating that the one-sided 95% confidence interval of the PFS rate at 28 months excludes 34.7%, 81 evaluable participants are required, where a treatment arm will be deemed a "success" if at least 37 out of 81 participants are progression-free at 28 months. To account for approximately 5% of participants being unevaluable at 28 months post-R<sub>3</sub>, 86 participants will be randomised to each treatment arm i.e. 172 participants are required to be entered into R<sub>3</sub>.

### *Total Study Sample Size*

Accounting for those participants who will be lost-to-follow-up R<sub>1</sub>, R<sub>2</sub> and R<sub>3</sub> require 500, 450, and 172 participants to enter each randomisation respectively.

Considering R<sub>1</sub> and R<sub>2</sub>, it is assumed that 50 participants will lose their MRD-negative status during the 12 months of continuous treatment (Myeloma XI, unpublished data). Therefore 550 participants are required to enter the MRD-negative part of the standard-risk pathway. It is assumed that 55% of standard-risk participants will be MRD-negative at the point of assessment therefore approximately 1000 participants are required to reach the MRD assessment stage of the standard-risk pathway [35, 39] It is assumed that 90% of all those recruited will reach this point therefore 1112 participants are required to enter the standard-risk pathway[5] . It is anticipated that 80% of all those recruited will be standard-risk (Myeloma XI, unpublished data) therefore at least 1390 participants are required to be recruited to the trial. Rounding this we obtain an overall sample size of 1400.

1  
2  
3  
4 This gives 280 participants who are expected to enter the high-risk pathway, using the same logic as  
5 in the standard-risk pathway if 90% of participants reach R3 then there will be approximately 252  
6 participants recruited to R3. Given the calculations above it is plausible that another arm could be  
7 added to the high-risk pathway at a later date.  
8  
9

#### 10 *Recruitment:*

11 It is planned that 1400 participants will be recruited for a total of 36 months. Once all centres are  
12 open, the recruitment target is 38 participants a month (equating to approximately 30 standard risk  
13 and 8 high-risk participants).  
14  
15  
16

17 In order to ensure the trial will meet the target sample size within the recruitment period, site set-up  
18 was prioritised whilst the trial was preparing to open to recruitment. In addition, the trial team are  
19 actively engaging with Principal Investigators at sites who support the trial to ensure that those sites  
20 open quickly and are maintaining regular communication with open sites to ensure that they continue  
21 to recruit to the trial.  
22  
23  
24

25 The trial opened to recruitment on 11/05/2021.  
26  
27

#### 28 **Assignment of treatment allocations:**

29 Each of the registration and randomisation procedures will be conducted centrally using the University  
30 of Leeds Clinical Trial Research Unit (CTRU) automated 24-hour web base and telephone system.  
31  
32

#### 33 **Registration**

34 If a patient is suspected to have myeloma they will enter the trial at the time of routine diagnostic  
35 tests, through bone marrow registration. Once diagnosis is confirmed locally and the research team  
36 consider the patient potentially eligible for the trial, patients will be provided with full verbal  
37 explanation of the trial and full participant information sheet and informed consent documents to  
38 consider. Once the patient has provided informed consent to the first stage of the trial they will be  
39 registered into the trial at Bone Marrow Registration.  
40  
41  
42  
43

44 Patients who have already had Myeloma confirmed prior to being approached for the trial, and those  
45 who decline consent at bone marrow registration, will enter at main trial registration.  
46  
47

#### 48 **Data Collection**

49 Data collection will primarily be via Remote Data Entry (RDE) on electronic case report forms (eCRFs),  
50 provided by the CTRU at the University of Leeds, and will be entered by staff at the research site.  
51 Access to the live RADAR database will be provided by the CTRU following sites being authorised to  
52 open to recruitment; guidance on RDE and completing eCRFs will be provided. Data regarding  
53 informed consent, QoL, Healthcare Resource Use questionnaires and in-patient stay forms will be  
54 collected via paper case report forms.  
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3 QoL and Healthcare Resource Use questionnaires will be completed by the participant in clinic or at  
4 home and sealed in an envelope before handing back to the site research team who will return them  
5 to the CTRU via post.  
6  
7

### 8 **Data Management**

9  
10 All information collected during the course of the trial will be kept strictly confidential. Information  
11 will be held securely on paper and electronically at the CTRU. The CTRU will comply with all aspects of  
12 the Data Protection Act 2018.  
13  
14

15 Data will be monitored for quality and completeness by the CTRU. Missing data will be chased until it  
16 is received, confirmed as not available or the trial is at analysis. The CTRU/Sponsor will reserve the  
17 right to intermittently conduct source data verification exercises on a sample of participants, which  
18 will be carried out by staff from the CTRU/Sponsor. Source data verification will involve direct access  
19 to participant notes at the participating hospital sites and the ongoing central collection of copies of  
20 Informed Consent Documents and other relevant investigation reports.  
21  
22

### 23 **Statistical methods**

24  
25 Statistical analysis is the responsibility of the CTRU statisticians, with the exception of the cost-  
26 effectiveness analysis, which will be undertaken by the health economists at the University of Leeds.  
27 A full statistical analysis plan (SAP) and Health Economics Analysis Plan (HEAP) will be written and  
28 approved before any analyses are undertaken.  
29  
30

31  
32 The analysis population will depend on the randomisation. Separate intention to treat (ITT), per  
33 protocol (PP) and safety populations will be defined for each randomisation. In either case the ITT  
34 population will include participants according to their randomisation allocation, regardless of  
35 eligibility whether they prematurely discontinued the treatment, or did not comply with the regimen.  
36 The PP population will exclude individuals who do not receive their randomisation allocation or who  
37 are found to be ineligible following randomisation. The safety population will consist of all participants  
38 who receive at least one dose of the trial treatments and analyse participants according to what they  
39 received rather than what they were randomised to.  
40  
41  
42

43  
44 With the exception of two interim analyses, no other formal analysis is planned until participants have  
45 attained the primary endpoint for each of the randomisations.  
46  
47

#### 48 *Primary endpoint analyses*

##### 49 Randomisation 1

50  
51 The primary endpoint for R1 will be attained 2 years after the final participant has been randomised  
52 to R1.  
53  
54

55 As R1 is a non-inferiority trial, both PP and ITT population analyses will be used as co-primary analyses  
56 and both are required to demonstrate statistical significance of non-inferiority where any  
57 discrepancies will be reported.  
58  
59  
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1  
2  
3 PFS at R1 will be assessed using Cox proportional hazards regression to adjust for the stratification  
4 factors of R1 excluding centre, and presented using Kaplan-Meier estimates of the survival function.  
5 The treatment cessation strategy will be declared non-inferior to the continuous treatment strategy  
6 if the upper bound of the one-sided 95% confidence interval for the hazard ratio is less than 1.38. Note  
7 no adjustment will be made for interim analysis due to it being a test for inferiority (see below) and  
8 not non-inferiority.  
9  
10

### 11 12 Randomisation 2

13 The primary endpoint for R2 will be attained 6 months after the final participant has been randomised  
14 to R2. Primary analysis will be undertaken on the ITT population.  
15  
16

17 An overall one-sided approximately 3% FWER will be applied accounting for each pair-wise  
18 comparison over each stage and all comparisons. This equates to a 25% and 1% one sided significance  
19 level at interim and final analysis. MRD-negative rate will be compared between each pair-wise  
20 comparison (experimental vs control) in turn using logistic regression and adjusted for the  
21 minimisation factors of R2 excluding centre.  
22  
23  
24

### 25 Randomisation 3

26 The primary endpoint for R3 will be attained 28 months after the final participant has been  
27 randomised to R3.  
28  
29

30 Primary analysis will be undertaken on the ITT population. The number of participants who are alive  
31 and progression-free at 28 months post R3 will be summarised separately within each treatment arm  
32 and exact one sided 95% confidence intervals calculated. The null hypothesis is that the percentage  
33 of participants alive and progression-free at 28 months post R3 is 34.7%. A treatment arm is deemed  
34 a "success" if the one sided 95% confidence intervals of the PFS rate at 28 months excludes 34.71%.  
35 The treatment will then be proposed to be investigated further in a phase III trial.  
36  
37  
38

39 No multiple imputation is planned for the primary endpoints.  
40  
41

### 42 *Secondary endpoint analyses*

43 Overall survival and other time-to-event endpoints will be analysed using methods similar to those  
44 described for progression-free survival. All binary endpoints will be analysed using similar methods to  
45 those described for the attainment of MRD negativity endpoint.  
46  
47

48 For both R1 and R3, each experimental arm will be independently compared to historical control data  
49 using molecularly matched individual participant data (IPD) from Myeloma XI+(TE) and assessed for  
50 superiority in terms of progression-free survival. Further details of the molecular matching of IPD will  
51 be described in the statistical analysis plan, but it is anticipated that propensity score matching may  
52 be an appropriate technique. In each case a one-sided 10% significance level will be applied for each  
53 comparison with historical data.  
54  
55  
56

57 The number and proportion of participants in each response category will be summarised by allocated  
58 treatment and exact 95% two-sided confidence intervals will be calculated. The difference in  
59  
60

1  
2  
3 proportions for each response category will be presented with corresponding 95% two-sided  
4 confidence intervals.  
5

6  
7 Quality of life will be summarised using mean scores adjusted for baseline and two-sided 95% CI for  
8 each EORTC QLQ-C30 and EORTC QLQ-MY20 module symptom, role and functioning domain at each  
9 assessment time-point. Similar summaries will be produced for quality-adjusted life years (QALYs) as  
10 scored by the EQ-5D 3 Level (EQ-5D-3L) questionnaire. For the key secondary analysis of R1, the Global  
11 Health Status / Quality of Life subscale at two years post-R1, will be compared between the arms using  
12 a multivariable linear regression model, adjusting for the R1 stratification factors.  
13  
14

#### 15 16 *Exploratory and subgroup analyses*

17 A series of subgroup and exploratory analyses will be undertaken. Subgroup analyses will follow the  
18 same structure as the main analysis of the respective endpoint. Where appropriate interaction terms  
19 will be added to the regression models to account for the subgroup being investigated. Subgroup and  
20 exploratory analyses may, by chance, generate false negative or positive results. Those carried out will  
21 be interpreted with caution.  
22  
23

24  
25 The analysis for the exploratory outcomes will be detailed in the SAP.  
26  
27

#### 28 **Health economics**

29 The economic evaluation will take a decision modelling approach to assess the cost-effectiveness of  
30 treatment options for risk stratified treatment vs standard non-stratified treatment over participants'  
31 lifetime. This will allow several research questions to be incorporated within one model. The model  
32 will be developed using best practice[40] and the model structure, health states and parameter values  
33 will be derived from the trial outputs, published literature, and expert clinical opinion. Data to model  
34 stratified treatment options will be drawn from the RADAR trial results while parameters for standard  
35 non-stratified treatment will be obtained from the wider literature.  
36  
37

38  
39 Reflecting the main trial analysis of effectiveness, the economic evaluation will assess the cost-  
40 effectiveness of treatment options at each of the randomisations in RADAR. For standard risk  
41 participants at R1, the cost-effectiveness analysis will compare treatment with isatuximab for 12 cycles  
42 only to long-term isatuximab treatment, continued until disease progression. For standard risk  
43 participants who are MRD-positive at 100 days post-ASCT in terms of conversion to MRD negativity at  
44 R2, the cost-effectiveness of post-ASCT consolidation and maintenance treatments in the treatment  
45 of standard-risk participants will be evaluated. For high-risk participants at R3, the cost-effectiveness  
46 of post-ASCT consolidation and maintenance treatment strategies containing lenalidomide,  
47 bortezomib, dexamethasone and isatuximab separately will be evaluated. In addition, the cost-  
48 effectiveness of stratified treatment pathways will be compared with standard non-stratified  
49 treatments.  
50  
51  
52  
53

54  
55 All analyses will be conducted following NICE reference case guidelines[41]. As such, outcomes will be  
56 measured in QALYs based on EQ-5D [42] and EORTC QLQ-C30 [43] utilities and costs will be calculated  
57 from a health and personal social services perspective. Cost-effectiveness will be determined in  
58 comparison to the NICE cost-effectiveness threshold of £20,000 per QALY gained. Deterministic and  
59 probabilistic (using Monte Carlo simulations) sensitivity analyses will be conducted to explore the  
60

1  
2  
3 impact of parameter value changes on estimates of cost-effectiveness and to determine the level of  
4 uncertainty around the results of the lifetime analysis. In addition, value of information analysis will  
5 be conducted to estimate the value of further research.  
6  
7

### 8 **Trial Oversight**

9  
10 The TMG includes the CI, CTRU team and co-investigators that are assigned responsibility for the  
11 clinical set up, ongoing management, promotion of the trial and interpretation of the results. The trial  
12 steering committee (TSC), consisting of independent clinicians and statisticians, will provide overall  
13 supervision on the trial, including trial progress, adherence to protocol, participant safety and  
14 consideration of new information.  
15  
16

### 17 **Data Monitoring**

18  
19 An independent data monitoring and ethic committee (DMEC) will review the safety and ethics of the  
20 trial. Detailed reports will be prepared by the CTRU for the DMEC meetings which will take place at  
21 approximately yearly intervals. Additional reports will also be provided at intervals between these  
22 meetings. The committee will also review cumulative safety data by arm on an ongoing basis along  
23 with individual SAE/SAR listings. After each annual review, the DMEC will make their  
24 recommendations to the TSC about the continuation of the trial.  
25  
26  
27

### 28 *Interim Analyses*

29  
30 Full interim reports will be presented to the DMEC in confidence annually and following the planned  
31 interim analyses which are expected to take place when half the number of events (119) have been  
32 observed in the treatment de-escalation pathway (R1) and at the end of the activity stage 1 treatment  
33 escalation pathway (R2), approximately 6 months after the 40<sup>th</sup> participant has been randomised.  
34  
35

36  
37 The interim analysis of R1 will be a one-sided test for inferiority conducted at the 5% significance level.  
38 PFS at R1 will be assessed using Cox proportional hazards regression to adjust for the minimisation  
39 factors (excluding centre), and presented using Kaplan-Meier estimates of the survival function.  
40  
41

42  
43 The interim analysis for R2 will be conducted at the end of Stage I (the phase II part) of the  
44 randomisation which is due 6 months following the randomisation of the 40<sup>th</sup> participant. This analysis  
45 will compare each experimental arm with the control arm in separate tests of superiority using a one-  
46 sided 25% significance level and 95% power to determine whether any of the experimental arms show  
47 lack of activity i.e. the null hypothesis in the superiority test is not rejected. Should an arm show lack  
48 of activity it will not be continued to the second stage of the randomisation (the phase III part). To  
49 account for the interim analysis and to give an overall significance level of 1% and power of 80% for  
50 each individual comparison the final analysis will be conducted using a one-sided 1% significance level  
51 and 85% power. Recruitment will continue seamlessly between activity and efficacy in these scenarios.  
52 Formal powered pair-wise comparisons are not undertaken comparing experimental arms at either  
53 stage.  
54  
55

56  
57 The DMEC committee members, in light of the interim analysis, will make their recommendations to  
58 the TSC about the continuation of the different aspects of the trial.  
59  
60

## Harms

### Adverse events

Adverse events are any untoward medical occurrence in a participant or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment. AEs can be defined as any unintentional, unfavourable clinical signs or symptoms; any new illness or disease, or the deterioration of existing disease or illness; or clinically relevant deterioration in any laboratory assessments or clinical test. Due to the nature of multiple myeloma and its treatment, participants are likely to experience several adverse events throughout the course of the disease.

All AEs, both related and unrelated to myeloma treatment will be collected on the relevant eCRF from trial registration until 60 days after the last dose of protocol treatment and will be evaluated in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events 5.0 (NCI-CTCAE). AEs and ARs should continue to be collected for participants who are randomised to 'stop isatuximab' at R1 (and until 60 days after last on-trial assessment), even though they will not be receiving any trial drugs during this period.

### Adverse Events of special interest

An AE of special interest (serious or non-serious) is one of scientific and medical concern specific to isatuximab, for which ongoing monitoring and rapid communication by the investigator to the sponsor is considered to be appropriate. Isatuximab AEs of special interest include;  $\geq$ Grade 3 infusion reactions (IRs), Pregnancies, Symptomatic overdoses with IMP, and Second Primary Malignancies (SPMs).

### Serious adverse events

Serious Adverse Events (SAEs) are defined as any untoward medical occurrence or effect that at any dose results in death; or are life threatening (at the time of the event); or require in-patient hospitalisation or prolongation of existing hospitalisation; or result in persistent or significant disability or incapacity; or result in a congenital anomaly or birth defect; or any other important medical event. All SAEs will be reported from registration until 60 days post the last dose of the trial drug. SAEs should continue to be collected for participants who are randomised to 'stop isatuximab' at R1 (and until 60 days after last on-study assessment), even though they will not be receiving any study drugs during this period.

Serious Adverse Reactions (SARs) are SAEs that are deemed possibly related to any dose administered of any trial treatment. Suspected unexpected serious adverse events (SUSARs) are SARs which are not listed in the reference safety information for that medicinal product. SARs and SUSARs will be reported from the date of first trial dose and for the duration of the trial.

### Secondary malignancies

All new primary malignancies (SPMs) or suspected malignancies occurring from the date of trial registration and for the duration of the trial will be recorded. SPMs will be summarised and reviewed by an appointed member of the TMG who will determine whether trial treatment should continue.

### Pregnancies

Participants registered into RADAR agree to follow the Celgene approved Pregnancy Prevention Programme. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease status) in a female participant must be reported throughout the study and for 12 months after the last dose of cyclophosphamide or for 5 months following cessation of protocol treatment, whichever is longest. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease status) in a male participant's partner must be reported throughout the study and for 6 months after the last dose of cyclophosphamide or for 5 months following cessation of protocol treatment, whichever is longest.

### *Safety Analyses*

Safety analyses will summarise all SUSARs, SARs, SAEs, AEs and ARs, respective to where they occurred within the trial pathway (Induction, ASCT, Pre-R1, Post-R1, Post-R2, Post-R3). Safety data will be presented by treatment group for the safety population in addition to relationship to trial treatment.

### *Auditing*

The CTRU and the trial sponsor have procedures in place to ensure that serious breaches of Good Clinical Practice (GCP) or the trial protocol are picked up and reported. A triggered monitoring plan will ensure that sites at risk are monitored accordingly.

### **Patient and Public Involvement**

RADAR has been developed following extensive discussion with the UK myeloma community. Patients were first involved into the research at the grant application stage, and were incorporated into the development of the primary endpoint of R1, in which they confirmed a research question involving the stopping of treatment given there was no detectable myeloma would be of interest. The trial consent and participant information documents were reviewed for clarity by a patient representative. To ensure that a patient perspective is considered throughout the trial a PPI advisory group, including 4-8 members will feed into TMG meetings, and plan to host quarterly meetings to discuss urgent matters. It is envisioned that the PPI group, may help with writing summaries of results that can be published on patient forums and websites and maybe even shared directly with patients.

### **Ethics and Dissemination**

#### **Research and ethics approval**

Ethics approval has been obtained from the London – Central Research Ethics Committee (20/LO/0238). In addition capacity and capability has been confirmed by the appropriate research and development department for each participating centre prior to opening to participant recruitment into the trial. This included but was not limited to; having access to the non-trial supplied IMP (Bor, Cy and D), being able to conduct FISH as SoC, capacity of staff, ability to complete all protocol required assessments/investigations, and ability to archive trials documents.

Participants will be required to provide informed consent before joining the trial.



## Protocol Amendments

The trial opened to recruitment on 11/05/2021 using protocol version 2, dated 29<sup>th</sup> April 2020. This publication is written based from protocol version 3 dated July 2021. An amendment to protocol version 3 is anticipated Mid-2022, which should include the following:

### *High-Risk Pathway*

The cytogenetic abnormality del(1p) will be added to the definition of high-risk. In addition, Isa will be added to induction regimen for high-risk patients following their first cycle of RCyBorD (whilst their risk status is confirmed). Furthermore, R3 will be removed and high-risk patients will receive RBorIsaD + RIsa only post-ASCT. The pathway will follow a single-arm, single stage, phase II, three outcome design, with the new primary objective to assess the activity of RCyBorD+Isa induction followed by ASCT and RBorD+Isa consolidation and RIsa maintenance in terms of PFS at 18 months post trial registration.

### *Other changes*

- The removal of the phone registration and randomisation;
- The clarification of allowing prescribed medication to remove risks of thromboembolism before preceding onto treatment in the exclusion criteria for registration (and for starting post ASCT treatment)
- The allowance of blood support products, blood transfusions and platelet transfusions as per institutional guidelines at eligibility and pre-treatment assessments
- An update of exclusion criteria to allow for previous plasmacytomas.

## Consent or assent

The PI retains overall responsibility for the informed consent of participants at their site and must ensure that any medically qualified person delegated responsibility to participate in the informed consent process is duly authorised, trained and competent to participate according to the ethically approved protocol, principles of GCP and Declaration of Helsinki. Written consent will be obtained and signed by a medically qualified member of the site research team. Informed consent must be obtained, and the participant must be registered into the trial prior to the participant undergoing procedures that are specifically for the purposes of the trial and are out-with standard routine care at the participating site. This include the confirmation of optional consent (QoL/ Healthcare resource use questionnaires and decision regarding consent for samples to be used in future research). At any stage, participants can withdraw consent without repercussion.

## Confidentiality

All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRU will comply with all aspects of the Data Protection Act 2018.

## Access to data

Individual participant data (with any relevant supporting material, e.g. data dictionary, protocol, statistical analysis plan) for all trial participants (excluding any trial-specific participant opt-outs) will be made available for secondary research purposes at the end of the trial, i.e. usually when all primary and secondary endpoints have been met and all key analyses are complete.

Data will be shared according to a controlled access approach, based on the following principles:

- The value of the proposal will be considered in terms of the strategic priorities of the CTRU, Chief Investigator and Sponsor, the scientific value of the proposed project, and the resources necessary and available to satisfy any data release request.
- We encourage a collaborative approach to data sharing, and believe it is best practice for researchers who generated datasets to be involved in subsequent uses of those datasets.
- The timing and nature of any data release must not adversely interfere with the integrity of the trial or research project objectives, including any associated secondary and exploratory research objectives detailed in the ethically approved original research protocol. On an individual trial or research project basis, a reasonable period of exclusivity will be agreed with the trial or research project team.
- Any data release must be lawful, in line with participants' rights and must not compromise patient confidentiality. Where the purposes of the project can be achieved by using anonymised or aggregate data this will always be used. We will release individual patient data only in a form adjusted so that recipients of the data cannot identify individual participants by any reasonably likely means. We will also only share data when there is a binding agreement in place stating that data recipients will not attempt to re-identify any individual participants.
- Any data release must be in line with any contractual obligations to which the CTRU is subject.
- The research must be carried out by a bone fide researcher with the necessary skills and resources to conduct the research project.
- The research project must have clear objectives and use appropriate research methods.
- The research must be carried out on behalf of a reputable organisation that can demonstrate appropriate IT security standards to ensure the data is protected and to minimise the risk of unauthorised disclosure.

Data will only be shared for participants who have given consent to use of their data for secondary research.

Requests to access trial data should be made to [CTRU-DataAccess@leeds.ac.uk](mailto:CTRU-DataAccess@leeds.ac.uk) in the first instance. Requests will be reviewed (based on the above principles) by relevant stakeholders. No data will be released before an appropriate agreement is in place setting out the conditions of release. The agreement will govern data retention requirements, which will usually stipulate that data recipients must delete their copy of the data at the end of the planned project.

## Ancillary and post-trial agreements

Participants who stop trial treatment due to progression or any point prior to the end of trial will be treated off-trial at the discretion of their treating clinician. Those who stop prior to disease progression will be followed up 2 monthly until disease progression, death or the end of the trial. Following disease progression all participants will be followed up annually until death, or until the end of the trial for post progression endpoints.

Participants in the R1 pathway who are MRD-positive at 12 months post 12 cycles of isotuximab and therefore aren't eligible for randomisation 1 will continue to receive isotuximab maintenance, these

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3 participants would continue to be monitored, and data collected, as previously but trial samples would  
4 not be collected.  
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### 6 7 **Dissemination policy**

8 Authorship will be in keeping with the UK-MRA publication policy and due acknowledgement to  
9 participants, local investigators, funders and NCRI Haematological Oncology Study Group support  
10 made. The success of the trial depends upon the collaboration of all participants. For this reason, credit  
11 for the main results will be given to all those who have collaborated in the trial, through authorship  
12 and contributor-ship. Uniform requirements for authorship for manuscripts submitted to medical  
13 journals will guide authorship decisions alongside the guidance of the UK Myeloma Research Alliance  
14 Authorship Policy.  
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19 To maintain the scientific integrity of the trial, data will not be released prior to the end of the trial or  
20 a primary endpoint being reached, either for trial publication or oral presentation purposes, without  
21 the permission of the Trial Steering Committee and the (Co-)Chief Investigators. In addition, individual  
22 collaborators must not publish data concerning their participants that is directly relevant to the  
23 questions posed in the trial until the main results of the trial have been published and following  
24 written consent from the Sponsor.  
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### 28 **Appendices**

#### 29 30 *Informed consent material*

31 The consent forms which are to be completed by the participant at Bone Marrow Registration and/or  
32 Trial Registration and prior to each randomisation pathways are included in supplementary material.  
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#### 35 36 *Biological specimens*

37 The collection of central samples for laboratory analysis is summarised in Figures 3 and 4. The analysis  
38 to be conducted for trial purposes is stated in the supplementary material. Additional analysis may be  
39 carried out by each central laboratory provided the appropriate consent for sample use in future  
40 research has been provided by the participant at trial entry.  
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#### 44 **Author Contributions**

45 The RADAR trial was conceived by KY and MC and designed by them in collaboration with DAC. All  
46 authors (KLR, ABC, KR, DAC, AH, SQ, MD, MK, RO, HWA, GC, DM, CO, LB, RL, AP, BD, MC, GP, RP, GJ,  
47 CB, JS, RT, AC, CP, MC, SA, and KY) inputted into the development of the protocol and participant  
48 information sheet. The first draft of the protocol paper was written by KLR and ABC. All authors (KLR,  
49 ABC, KR, DAC, AH, SQ, MD, MK, RO, HWA, GC, DM, CO, LB, RL, AP, BD, MC, GP, RP, GJ, CB, JS, RT, AC,  
50 CP, MC, SA, and KY) reviewed and approved the final manuscript.  
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53

#### 54 **Funding**

55 This trial is funded by Cancer Research UK (C9203/A24078), Sanofi Genzyme and Celgene: A BMS  
56 Company. The funders had no role in the design, collection, analysis or collection of data; in writing  
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3 the manuscript; or in the decision to submit the manuscript for publication. This work was also  
4 supported by Core Clinical Trials Unit Infrastructure from Cancer Research UK (C7852/A25447).  
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7 The trial sponsor is responsible for the overall conduct of the trial as defined by Directive 2001/20/EC  
8 is University of Leeds, UoL/LTHT Joint Sponsor QA office (CTIMPs); Research & Innovation  
9 Centre/Faculty of Medicine & Health; Leeds Teaching Hospitals NHS Trust/University of Leeds; St  
10 James University Hospital; Leeds LS9 7TF.  
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### 14 **Competing Interest Statement**

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16 ABC, KLR, DAC, AH, CO, LBai, LBar, AP, RL report grants and non-financial support from BMS/Celgene,  
17 grants and non-financial support from Merck Sharpe & Dohme, grants and non-financial support from  
18 Amgen, grants and non-financial support from Takeda, during the conduct of the trial. DAC also  
19 reports travel support from Celgene Corporation.  
20  
21  
22

23 KY, RDT, CB, GJ, GP, MC, BD, DM, GC, HA, KR,SA, AC have no conflicting interests to declare. MC  
24 declares, Bristol Myers Squibb- employee, Honoraria/travel support in the last 3 years from, Amgen  
25 ,BMS/Celgene, Janssen, Takeda, Abbvie. CP declares BMS/Celgene Ad boards and speaker fees, Sanofi  
26 – Ad board, speaker fees, conference registration fees. JS reports Carrying out consultancy work  
27 (Advisory Board) for Sanofi. And an educational speaking engagement for Celgene/BMS RP declares;  
28 Honoraria – Janssen, BMS, Abbvie, GSK. Consultancy: GSK, Janssen. Meeting support: Janssen,  
29 Takeda, BMS. RO declares- Janssen - advisory board, honoraria, Celgene – honoraria, Beigene -  
30 advisory board, honoraria, Astra Zeneca – honoraria. MK declares inter-relationships: AbbVie:  
31 consultancy; Amgen: honoraria; BMS/Celgene: consultancy, research funding (institution); GSK:  
32 consultancy; Janssen: consultancy, research funding (institution); Karyopharm: consultancy; Pfizer:  
33 consultancy; SeattleGenetics: consultancy; Takeda: consultancy; Sanofi: honoraria. MD reports  
34 owning stock in Abingdon Health. SQ is the founder and CSO of Achilles therapeutics a company  
35 developing T cell therapies for solid tumours.  
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3 **Figure Legends/ Captions**

4 Figure 1: Flow chart of participant’s timelines in the RADAR study

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6 Figure 2: Schedule of local investigations

7 Figure 3: Central Investigations from diagnosis up to 100 days post-ASCT

8 Figure 4: Central Investigations for the R1, R2 and R3 pathways  
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For peer review only



Figure 1: Flowchart of Participants timelines in the RADAR Study

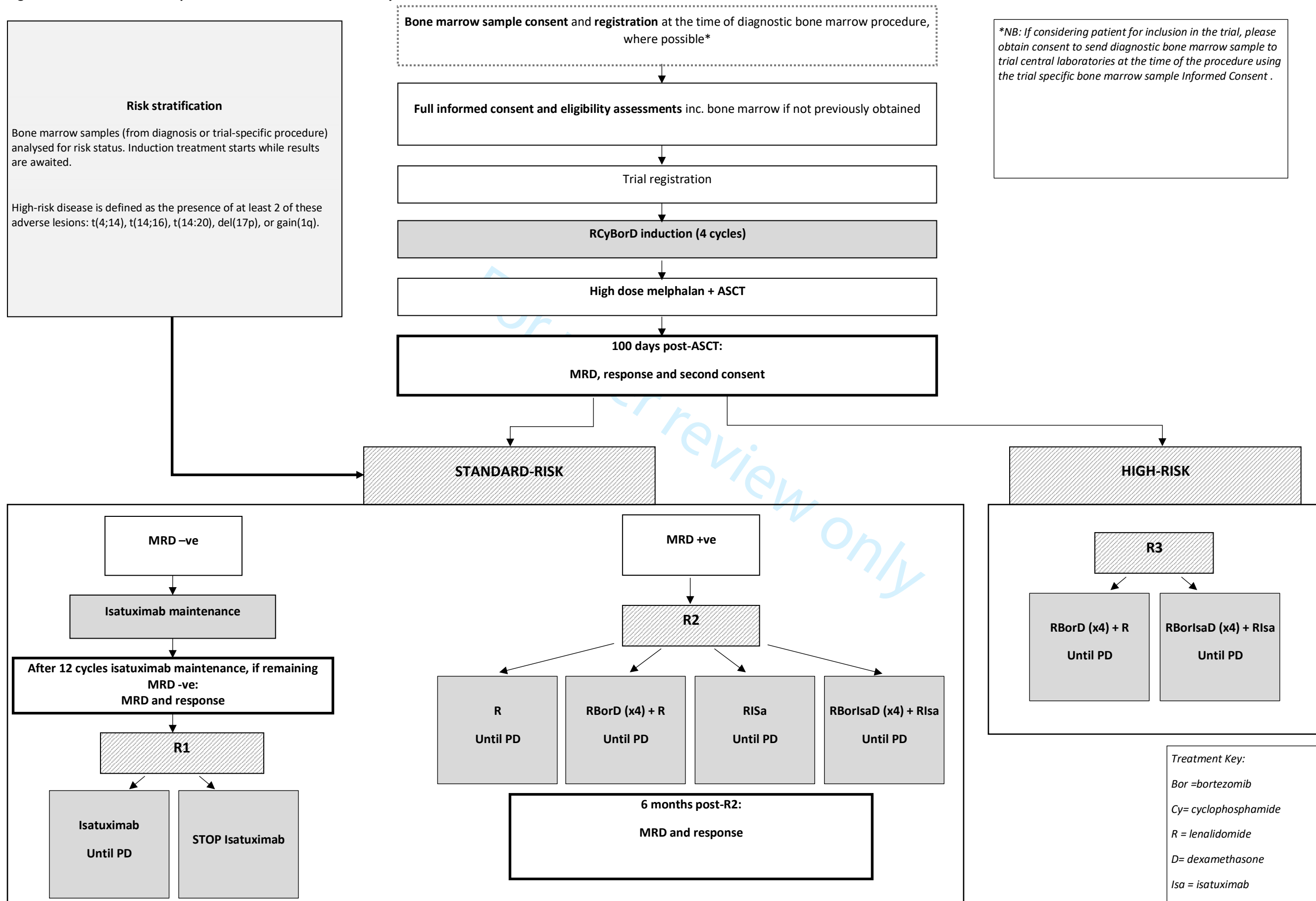


Figure 2: Schedule of Local Investigations

	RCyBorD Induction – All participants				R1 treatment pathway			R2 and R3 treatment pathway R2 participants on R or R1sa arm: After 3,6,12 and 18 cycles**		
	Pre-registration/baseline (within 14 days prior to registration, unless otherwise stated)	Day 1 (or day -1) of each cycle during RCyBorD induction††	End of RCyBorD induction	100 days post-ASCT (within 14 days prior to R2, start of Isatuximab maintenance or R3)	Day 1 of each cycle of isatuximab treatment††	On the day of isatuximab dose††	Follow up for participants coming off study during R1 treatment pathway: every 2 months	Day 1 of each cycle of treatment††	On day of (and prior to) every isatuximab dose††	Follow up for participants coming off study during R2/R3 treatment pathway: every 2 months
Written informed consent	✓ Consent to be taken prior to all assessments, permitted outside the 14-day window			✓ (permitted outside the 14-day window)						
Physical examination	✓	✓	✓	✓	✓			✓		
ECOG	✓	✓	✓	✓	✓			✓		
Covid vaccination status	✓	✓	✓	✓	✓		✓	✓		✓
Medical history (including review for prior cancers and history of Covid infection)	✓		✓	✓						
Assessment of cardiac risk*	✓(results from formal measurements within 28 days prior to registration)	If clinically indicated	✓	If clinically indicated	If clinically indicated			If clinically indicated		
ECG					Every 3 months in participants receiving Isatuximab			Every 3 months in participants receiving Isatuximab		
Thyroid function monitoring*	✓(within 28 days prior to registration)	If clinically indicated	✓	If clinically indicated	If clinically indicated			If clinically indicated		
FBC, LFTs, albumin, LDH, U&Es, calcium, and creatinine¶	✓	✓	✓	✓	✓	✓ FBC, U&E and creatinine only		✓	✓ FBC, U&E and creatinine only	
Hepatitis B, (surface antigen and core antibody), ,hepatitis C and HIV	⊠(within 28 days prior to registration)									
β2-microglobulin (β2M)	✓									
C-Reactive protein (CRP)	✓									
Calculated creatinine clearance (using Cockcroft-Gault formula)	✓	✓	✓	✓	✓			✓		
Serum paraprotein and immunofixation, serum free light chains and urinary free light chain detection	✓	✓	✓	✓	✓		✓ (if performed as part of standard care)	✓		✓ (If performed as standard of care)
Bone marrow (aspirate and trephine) See Table below for details of central investigations	✓ (within 6 weeks prior to registration)	✓(recommended only if a first occurrence of CR or SCR is suspected)	✓	✓	✓(recommended only if a first occurrence of CR or sCR is suspected)		✓ (if performed as part of standard care)	✓ (recommended only if first occurrence of CR/SCR is suspected)		✓ (If performed as standard of care)
Pregnancy prevention counselling	✓	At least every 28 days during lenalidomide treatment								
Pregnancy test† (for females of childbearing potential)	✓	✓‡			✓				✓‡	
Cross-sectional imaging according to local practice, to include the thorax (low dose whole body CT recommended)	Within 3 months before registration§	If clinically indicated. †			If clinically indicated			If clinically indicated		
Assessment of adverse events (including adverse events and second primary malignancy)		Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose)			Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose) . AEs should continue to be monitored for participants randomised to 'stop Isatuximab' at R1 (and until 60 days after last on-study assessment).			Monitor throughout study and report on relevant treatment eCRFs (from first treatment dose until 60 days post last treatment dose)		

\*Performed as part of standard of care.  
\*\* ECGs should be scheduled to align with other required face-to-face visits  
¶ The FBC should be repeated mid-cycle 1 (Day 14 +/-3 days) or more frequently and during subsequent cycles if there is a concern about cytopenias  
† Females of childbearing potential (FCBP) must have a negative pregnancy test performed by a healthcare professional in accordance with the Celgene Lenalidomide Pregnancy Prevention Plan  
‡‡ May be performed within the 48 hours prior to the specified day  
‡‡‡ In addition to standard Day 1 assessments  
‡ All FCBP: The first pregnancy test must be performed within 10 to 14 days prior to the start of lenalidomide and the second pregnancy test must be performed within 24 hours prior to the start of lenalidomide.  
FCBP with regular or no menstrual cycles: within 24 hours before start of lenalidomide treatment; weekly for the first 28 days of study participation; 4-weekly as a minimum during lenalidomide treatment; at study discontinuation; and 4 weeks after last dose of lenalidomide  
FCBP with irregular menstrual cycles: within 24 hours before start of lenalidomide treatment; weekly for the first 28 days of study participation; 2-weekly as a minimum during lenalidomide treatment; at study discontinuation; and at 2 and 4 weeks after last dose of lenalidomide

**N.B. During the COVID-19 pandemic, face-to-face assessments must be carried out at least at the beginning of cycles 1 and 2 and at the end of consolidation. Subsequently, participants must be seen by a clinician at least every 3 cycles (and more frequently if clinically indicated or there are concerns).**

Figure 3: Central Investigations from diagnosis up to 100 days post-ASCT

Sample	Investigation	Diagnosis (if patient consented on NHS form and trial bone marrow Informed Consent Document) <sup>1</sup>	Baseline (post trial consent and before the start of treatment)	Day 1 of Cycle 1 RCyBorD induction	End of induction cycle 1	End of induction cycle 2	End of RCyBorD induction	100 days post-ASCT and prior to consolidation/maintenance
0.5-1 mL EDTA bone marrow aspirate <b>SEND TO HMDS, LEEDS</b>	Minimal Residual Disease	✓	✓ (if not sent previously)				✓	✓
10 mL clotted peripheral blood Random urine sample <b>SEND TO BIRMINGHAM</b>	Disease parameters (including paraproteins) for response assessments and covid-19 antibody response M-protein interference assay		✓	✓ Only if baseline sample not within 14 days	✓	✓	✓	✓
10 mL EDTA bone marrow aspirate 10 mL blood <b>SEND TO UCL, LONDON</b>	Tumour DNA for neoantigens cfDNA Immune profiling	✓ Bone marrow only	✓ BMA (if not sent previously) & blood	✓ Cycle 1 only 10 mL blood (only if baseline sample is not from within 14 days prior to cycle 1 day 1)				✓
Bone marrow trephine (6 sections) <b>SEND TO UCL, LONDON</b>	Immunostaining for immune function	✓	✓ (if not sent previously)					✓

Trial consent  
Consented to Myeloma XV trial and central laboratory investigations

<sup>1</sup> Baseline bone marrow samples may be taken before trial consent, provided that patients have consented to these samples being taken using the standard NHS consent form. The patient must have provided written informed trial consent on the trial bone marrow Informed Consent Document before these samples can be sent to the central laboratories.

Figure 4: Central Investigations for the R1, R2 and R3 pathways

Sample	Investigation	Standard-risk MRD-negative participants (R1 pathway)	Standard-risk MRD-positive participants on R or R1sa arm (R2 pathway)			Standard-risk MRD-positive participants on RBorD+R or RBor1saD+R1sa arm (R2 pathway)			High-risk participants (R3 pathway)			All participants
			After cycle 3	After cycles 6, 12 and 18	After cycle 24	After consolidation cycle 4	After maintenance cycles 3, 9 and 15	After maintenance cycle 21	After consolidation cycle 4	After maintenance cycles 3, 9 and 15	After maintenance cycle 21	
		After cycles 6, 12 and 24 of maintenance (or at equivalent time-points if randomised to stop receiving 1sa)										Disease progression
0.5-1 mL EDTA bone marrow aspirate SEND TO HMDS, LEEDS	Minimal Residual Disease	✓	✓	✓		✓	✓		✓	✓		✓
10 mL clotted peripheral blood Random urine sample SEND TO BIRMINGHAM	Disease parameters (including paraproteins) for response assessments and covid-19 antibody response M-protein interference assay	✓	✓	✓	✓ (blood only)	✓	✓	✓ (blood only)	✓	✓	✓ (blood only)	✓
10 mL EDTA bone marrow aspirate 10 mL blood SEND TO UCL, LONDON	Tumour DNA for neoantigens cfDNA Immune profiling	✓ (only after 6 cycles)	✓			✓			✓			✓
Bone marrow trephine SEND TO UCL, LONDON	Immuno-chemistry for immune function		✓			✓			✓			✓

## **RADAR: Protocol Paper Attachments**

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## 1 Glossary of Terms

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6	AE	Adverse event
7	ALT	Alanine aminotransferase
8	ANC	Absolute neutrophil count
9	AR	Adverse reaction
10	ASCT	Autologous stem cell transplantation
11	β2M	Beta2-microglobulin
12	BD	Twice daily
13	CI	Chief Investigator
14	CR	Complete response
15	CRF	Case report form
16	CRUK	Cancer Research United Kingdom
17	CTCAE	Common Terminology Criteria for Adverse Events
18	CTRU	Clinical Trials Research Unit
19	Cy	Cyclophosphamide
20	D	Dexamethasone
21	DMEC	Data Monitoring and Ethics Committee
22	DSUR	Developmental Safety Update Report
23	ECOG	Eastern Cooperative Oncology Group
24	eCRF	Electronic Case Report Form
25	EORTC	European Organisation for Research and Treatment of Cancer
26	FISH	Fluorescence in situ hybridization test
27	FWER	Family-wise error rate
28	GCP	Good Clinical Practice
29	HDM	High-dose melphalan
30	HMDs	Haematological Malignancy Diagnostic Service
31	IMiD®	Immunomodulatory Drug
32	IMP	Investigational medicinal product
33	IMWG	International Myeloma Working Group
34	IPD	Individual participant data
35	Isa	Isatuximab
36	ISS	International Staging System
37	ITT	Intention to treat
38	LFT	Liver function test
39	MedDRA	Medical Dictionary for Regulatory Activities
40	mg	Milligram
41	MGUS	Monoclonal gammopathy of undetermined significance
42	MHRA	Medicines and Healthcare Products Regulatory Agency
43	MM	Multiple myeloma
44	MR	Minimal response
45	MRD	Minimal Residual Disease
46	NCRI	National Cancer Research Institute
47	NDMM	Newly diagnosed multiple myeloma
48	NICE	National Institute for Health and Care Excellence
49	OS	Overall survival
50	PD	Progressive disease
51	PFS	Progression-free survival
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3	PFS2	Time to second progression
4	PI	Principal Investigator
5	PIS	Patient Information Sheet
6	PP	Paraprotein
7	PR	Partial response
8	PS	Performance status
9	QoL	Quality of life
10	R	Lenalidomide
11	R1-3	Randomisation 1-3
12	RCT	Randomised controlled trials
13	RDE	Remote Data Entry
14	REC	Research Ethics Committee
15	R-ISS	Revised International Staging System
16	RSI	Reference Safety Information
17	SC	Sub-cutaneous
18	SD	Stable disease
19	SAE	Serious adverse event
20	SAP	Statistical analysis plan
21	SAR	Serious adverse reaction
22	SmPC	Summary of Product Characteristics
23	SOP	Standard operating procedure
24	SPM	Secondary Primary Malignancy
25	SSOP	Study site operating procedure
26	SUSAR	Suspected unexpected serious adverse reaction
27	TE	Transplant eligible
28	TMG	Trial Management Group
29	TNE	Transplant non-eligible
30	TSC	Trial Steering Committee
31	U&Es	Urea & electrolytes
32	UK-MRA	United Kingdom Myeloma Research Alliance
33	ULN	Upper limit of normal
34	VGPR	Very good partial response
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## 2 List of Sites in the RADAR Trial

Aberdeen Royal Infirmary	Royal Bournemouth Hospital	University Hospital Wishaw
Royal Sussex County Hospital	Poole General Hospital	St Richard's Hospital
Chesterfield Royal Hospital	Salisbury District Hospital	Worthing Hospital
Derriford Hospital	Sunderland Royal Hospital	The Christie
Kent & Canterbury Hospital, Canterbury	South Tyneside District Hospital	Cheltenham General Hospital
Queen Elizabeth the Queen Mother Hospital	Southmead Hospital Bristol	Gloucestershire Royal Hospital
William Harvey Hospital	St. Helens	The Clatterbridge Centre
Freeman Hospital	Whiston Hospital	
Queen Elizabeth Hospital Gateshead	St George's Hospital (Tooting)	
Hammersmith Hospital	Torbay Hospital	
Manchester Royal Infirmary	University College London Hospital	
Wythenshawe Hospital	Leicester Royal Infirmary	
Milton Keynes University Hospital	Worcestershire Royal Hospital	
Perth Royal Infirmary	Alexandra Hospital, Redditch	
Ninewells Hospital	York Hospital	
Northampton General Hospital	University Hospital of Wales, Cardiff	
Churchill Hospital	Stratford Hospital	
Horton General Hospital	Warwick Hospital	
Queen Alexandra Hospital, Portsmouth	New Cross Hospital	
Queen Elizabeth Hospital, Birmingham	University Hospital Coventry	
Raigmore Hospital, Inverness	University Hospital Monklands	
Rotherham General Hospital	University Hospital Hairmyres	



### 3 Spirit Checklist: Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. *BMJ*. 2013;346:e7586

		Reporting Item	Page Number
<b>Administrative information</b>			
Title	<a href="#">#1</a>	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	<a href="#">#2a</a>	Trial identifier and registry name. If not yet registered, name of intended registry	1,2,3
Trial registration: data set	<a href="#">#2b</a>	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	<a href="#">#3</a>	Date and version identifier	29
Funding	<a href="#">#4</a>	Sources and types of financial, material, and other support	32
Roles and responsibilities: contributorship	<a href="#">#5a</a>	Names, affiliations, and roles of protocol contributors	1, 31
Roles and responsibilities: sponsor contact information	<a href="#">#5b</a>	Name and contact information for the trial sponsor	31,32
Roles and responsibilities: sponsor and funder	<a href="#">#5c</a>	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	32
Roles and responsibilities: committees	<a href="#">#5d</a>	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	26,27
<b>Introduction</b>			
Background and rationale	<a href="#">#6a</a>	Description of research question and justification for undertaking the trial, including summary of relevant	6,7

1				
2				
3			studies (published and unpublished) examining	
4			benefits and harms for each intervention	
5				
6	Background and	<a href="#">#6b</a>	Explanation for choice of comparators	6,7
7	rationale: choice of			
8	comparators			
9				
10	Objectives	<a href="#">#7</a>	Specific objectives or hypotheses	7, 18
11				
12	Trial design	<a href="#">#8</a>	Description of trial design including type of trial (eg,	8
13			parallel group, crossover, factorial, single group),	
14			allocation ratio, and framework (eg, superiority,	
15			equivalence, non-inferiority, exploratory)	
16				
17	<b>Methods:</b>			
18	<b>Participants,</b>			
19	<b>interventions, and</b>			
20	<b>outcomes</b>			
21				
22				
23	Study setting	<a href="#">#9</a>	Description of study settings (eg, community clinic,	8
24			academic hospital) and list of countries where data	
25			will be collected. Reference to where list of study sites	
26			can be obtained	
27				
28	Eligibility criteria	<a href="#">#10</a>	Inclusion and exclusion criteria for participants. If	8-14
29			applicable, eligibility criteria for study centres and	
30			individuals who will perform the interventions (eg,	
31			surgeons, psychotherapists)	
32				
33				
34	Interventions:	<a href="#">#11a</a>	Interventions for each group with sufficient detail to	15-17
35	description		allow replication, including how and when they will be	
36			administered	
37				
38	Interventions:	<a href="#">#11b</a>	Criteria for discontinuing or modifying allocated	17
39	modifications		interventions for a given trial participant (eg, drug	
40			dose change in response to harms, participant	
41			request, or improving / worsening disease)	
42				
43				
44	Interventions:	<a href="#">#11c</a>	Strategies to improve adherence to intervention	17
45	adherence		protocols, and any procedures for monitoring	
46			adherence (eg, drug tablet return; laboratory tests)	
47				
48	Interventions:	<a href="#">#11d</a>	Relevant concomitant care and interventions that are	17
49	concomitant care		permitted or prohibited during the trial	
50				
51	Outcomes	<a href="#">#12</a>	Primary, secondary, and other outcomes, including the	18
52			specific measurement variable (eg, systolic blood	
53			pressure), analysis metric (eg, change from baseline,	
54			final value, time to event), method of aggregation (eg,	
55			median, proportion), and time point for each	
56			outcome. Explanation of the clinical relevance of	
57			chosen efficacy and harm outcomes is strongly	
58			recommended	
59				
60				

Participant timeline	<a href="#">#13</a>	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	18,19
Sample size	<a href="#">#14</a>	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	20
Recruitment	<a href="#">#15</a>	Strategies for achieving adequate participant enrolment to reach target sample size	23

## Methods:

### Assignment of interventions (for controlled trials)

Allocation: sequence generation	<a href="#">#16a</a>	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	23
Allocation concealment mechanism	<a href="#">#16b</a>	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	23
Allocation: implementation	<a href="#">#16c</a>	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	23
Blinding (masking)	<a href="#">#17a</a>	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
Blinding (masking): emergency unblinding	<a href="#">#17b</a>	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA

### Methods: Data collection, management, and analysis

Data collection plan	<a href="#">#18a</a>	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires,	23
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3		laboratory tests) along with their reliability and	
4		validity, if known. Reference to where data collection	
5		forms can be found, if not in the protocol	
6			
7	Data collection plan: retention	<a href="#">#18b</a> Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	23
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12	Data management	<a href="#">#19</a> Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	23
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20	Statistics: outcomes	<a href="#">#20a</a> Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	18
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26	Statistics: additional analyses	<a href="#">#20b</a> Methods for any additional analyses (eg, subgroup and adjusted analyses)	24
27			
28			
29	Statistics: analysis population and missing data	<a href="#">#20c</a> Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	24
30			
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34	<b>Methods:</b>		
35	<b>Monitoring</b>		
36			
37	Data monitoring: formal committee	<a href="#">#21a</a> Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	27
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46	Data monitoring: interim analysis	<a href="#">#21b</a> Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	27
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52	Harms	<a href="#">#22</a> Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	27
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57	Auditing	<a href="#">#23</a> Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	29
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## Ethics and dissemination

1				
2				
3	<b>Ethics and</b>			
4	<b>dissemination</b>			
5				
6	Research ethics	<a href="#">#24</a>	Plans for seeking research ethics committee /	29
7	approval		institutional review board (REC / IRB) approval	
8				
9	Protocol	<a href="#">#25</a>	Plans for communicating important protocol	29
10	amendments		modifications (eg, changes to eligibility criteria,	
11			outcomes, analyses) to relevant parties (eg,	
12			investigators, REC / IRBs, trial participants, trial	
13			registries, journals, regulators)	
14				
15	Consent or assent	<a href="#">#26a</a>	Who will obtain informed consent or assent from	30
16			potential trial participants or authorised surrogates,	
17			and how (see Item 32)	
18				
19				
20	Consent or assent:	<a href="#">#26b</a>	Additional consent provisions for collection and use of	30,31
21	ancillary studies		participant data and biological specimens in ancillary	
22			studies, if applicable	
23				
24	Confidentiality	<a href="#">#27</a>	How personal information about potential and	30
25			enrolled participants will be collected, shared, and	
26			maintained in order to protect confidentiality before,	
27			during, and after the trial	
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30	Declaration of	<a href="#">#28</a>	Financial and other competing interests for principal	32
31	interests		investigators for the overall trial and each study site	
32				
33	Data access	<a href="#">#29</a>	Statement of who will have access to the final trial	30
34			dataset, and disclosure of contractual agreements that	
35			limit such access for investigators	
36				
37	Ancillary and post	<a href="#">#30</a>	Provisions, if any, for ancillary and post-trial care, and	32
38	trial care		for compensation to those who suffer harm from trial	
39			participation	
40				
41	Dissemination	<a href="#">#31a</a>	Plans for investigators and sponsor to communicate	31
42	policy: trial results		trial results to participants, healthcare professionals,	
43			the public, and other relevant groups (eg, via	
44			publication, reporting in results databases, or other	
45			data sharing arrangements), including any publication	
46			restrictions	
47				
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49	Dissemination	<a href="#">#31b</a>	Authorship eligibility guidelines and any intended use	31
50	policy: authorship		of professional writers	
51				
52	Dissemination	<a href="#">#31c</a>	Plans, if any, for granting public access to the full	31
53	policy: reproducible		protocol, participant-level dataset, and statistical code	
54	research			
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57	<b>Appendices</b>			
58	Informed consent	<a href="#">#32</a>	Model consent form and other related documentation	(Supplementary
59	materials		given to participants and authorised surrogates	Material)
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Biological specimens [#33](#) Plans for collection, laboratory evaluation, and storage (Supplementary  
of biological specimens for genetic or molecular Material)  
analysis in the current trial and for future use in  
ancillary studies, if applicable

None The SPIRIT Explanation and Elaboration paper is distributed under the terms of the Creative  
Commons Attribution License CC-BY-NC. This checklist can be completed online using  
<https://www.goodreports.org/>, a tool made by the [EQUATOR Network](#) in collaboration with [Penelope.ai](#)

For peer review only

#### 4 Excluded Concomitant Medication:

##### Excluded concomitant Medication:

1. Systemic treatment with any of the following metabolising enzyme inducers and inhibitors should be avoided, unless there is no appropriate alternative medication for the participant's use (if there were to be a drug-drug interaction with an inducer, cyclophosphamide and bortezomib metabolite exposure would be increased):
  - a. Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital
  - b. Strong CYP3A inhibitors
2. Excluded foods and dietary supplements include St. John's Wort, green tea and supplements containing green tea extracts
3. The following medicinal products and procedures are **prohibited** during this study:
  - a. Any antineoplastic treatment with activity against MM, other than study drugs
  - b. Platelet transfusions within 3 days prior to study drug dosing for any dosing day, or prior to randomisation in order to meet eligibility criteria.
  - c. Additional steroid therapy (not as trial IMP) (except before commencing trial treatment up to a maximum of 160mg dexamethasone equivalent as per inclusion criteria or steroids used to manage hypersensitivity to trial medication)
  - d. Radiotherapy for the treatment of symptoms related to disease progression.
  - e. Continuous use of clarithromycin (short courses of 5-10 days are permitted for treatment of infective episodes when indicated)
  - f. Hormone replacement therapy and erythropoietic agents and other agents that increase the risk of thrombosis (applicable during treatment with lenalidomide)

## ***Quality of Life and Health Economics questionnaires***

### **Timepoints for all participants up to 100 days post-ASCT**

- Baseline
- End of induction
- 100 days post-ASCT

### **\*R1 pathway participants**

- After cycles 6, 12, 24 and 36 (for participants randomised to 'stop isatuximab' at R1, the cycle 24 and 36 questionnaires should still be completed at equivalent timepoints)

### **\*Timepoints for R2 and R3 pathway participants receiving R or RIsa**

- After cycles 6, 12 and 24 of maintenance

### **\*Timepoints for R2 and R3 pathway participants receiving RBorD+R or RBorIsaD+RIsa**

- After cycles 3, 9 and 21 of maintenance.

*\*Note that participants who stop trial treatment should complete QoL at the equivalent time points (unless the participant wishes to withdraw consent for any further data collection)*



## 5 Exploratory analysis

Exploratory analysis will consider; the effect of post-ASCT consolidation regimens utilising combinations of lenalidomide, bortezomib, dexamethasone, and isatuximab on immune function in the bone marrow of participants following ASCT, using high dimensional characterisation of the immune microenvironment, immune subsets, phenotype and transcriptome; T cell receptor (TCR) repertoire in the bone marrow of participants following ASCT and consolidation and/or maintenance; correlation of baseline immune profile, TCR diversity and function with disease response, including MRD status and timing of disease relapse; ex-vivo functional studies with participant derived samples used to generate explants or immune-competent patient derived xenografts (icPDX); and to review infection and re-infection rates of COVID-19 in participants during induction, post-ASCT and during post-ASCT consolidation and maintenance treatment. All exploratory analysis to be conducted by the trial statisticians will be pre-specified in the statistical analysis plan.

## 6 Subgroup analysis

Subgroup analysis will be conducted to determine whether a selection of patient characteristics, haematology / local serological results, biochemistry results and cytogenetic/molecular results as well as response assessments (full list below) are prognostic of the endpoints; PFS, PFS2, OS, attainment of  $\geq$ VGPR and attainment of MRD negativity, as defined for all randomisations. Note that the subgroups listed under the Response subheading will not be analysed for the last two endpoints.

### Patient Characteristics

- Age (years) at trial registration ( $\leq 65$ ,  $>65$ )
- Sex (Male / Female)
- ECOG performance status at trial registration (0, 1,  $\geq 2$ )
- ISS at trial registration (Stage I, Stage II, Stage III)
- R-ISS at trial registration (Stage I, Stage II, Stage III)

### Haematology / Local Serological Results

- Haemoglobin concentration at trial registration ( $<100$ ,  $\geq 100$  g/L)
- Platelets at trial registration ( $<150$ ,  $\geq 150 \times 10^9$ /L)
- White blood cells at trial registration ( $< LLN$  (Lower limit of normal),  $\geq LLN$ )
- Neutrophil count at trial registration ( $< LLN$ ,  $\geq LLN$ )
- Lymphocyte count at trial registration ( $< LLN$ ,  $\geq LLN$ )
- Plasma cells (%) in bone marrow at trial registration ( $<60\%$ ,  $\geq 60\%$ )

### Biochemistry Results

- $\beta$ -2 microglobulin concentration at trial registration ( $<3.5$ ,  $3.5$ – $<5.5$ ,  $\geq 5.5$  mg/L)
- Serum creatinine concentration at trial registration ( $<175$ ,  $\geq 175$   $\mu$ mol/L)
- Corrected serum calcium concentration at trial registration ( $<2.75$ ,  $\geq 2.75$  mmol/L)
- Serum albumin at trial registration ( $<ULN$  (Upper limit of normal) ,  $\geq ULN$ )
- Lactate dehydrogenase at trial registration ( $<ULN$ ,  $\geq ULN$ )
- C-Reactive protein at trial registration ( $<ULN$ ,  $\geq ULN$ )
- Serum bilirubin at trial registration ( $<ULN$ ,  $\geq ULN$ )
- ALT/AST at trial registration ( $<ULN$ ,  $\geq ULN$ )

### Cytogenetic/molecular Results

- t(4,14) at trial registration (detected, not detected)
- t(14,16) at trial registration (detected, not detected)
- t(14,20) at trial registration (detected, not detected)
- del(17p) at trial registration (detected, not detected)
- 1q gain at trial registration (detected, not detected)
- Hyperdiploidy at trial registration (detected, not detected)
- The number of high-risk adverse lesions at trial registration (R1 and R2: 0, 1 unable to determine, R3: 2,  $\geq 3$ , or unable to determine)

### Response

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3 - Response to RCyBorD induction (<VGPR, ≥ VGPR)  
4 - Response at 100 days post-ASCT (<VGPR, ≥ VGPR)  
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6 - Response at the end of consolidation (<VGPR, ≥ VGPR)  
7 - Response to 12m post-ASCT treatment (<VGPR, ≥ VGPR)  
8 - MRD response to RCyBorD induction (R3 Only: MRD positive, MRD Negative)  
9 - MRD at 100 days post-ASCT (R3 Only: MRD positive, MRD negative)  
10 - MRD response to 6m post-ASCT treatment (R3 Only: MRD positive, MRD Negative)  
11 - MRD response to 12m post-ASCT treatment (R3 Only MRD positive, MRD Negative)  
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15 Further subgroup analyses may be undertaken, as appropriate and all the subgroups will be fully  
16 defined within the statistical analysis plan according to the current criteria [1-3].  
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## 7 Informed Consent Material

### *Bone Marrow Consent*

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number :
EudraCT Number:	Principal Investigator:



## **RADAR (UK-MRA Myeloma XV)**

### **INFORMED CONSENT DOCUMENT FOR BONE MARROW AND BLOOD SAMPLE**

**Please initial  
each box**

1. I confirm that I have read and understand the information sheet for the bone marrow sample request and have had the opportunity to ask questions.
2. I understand that my providing bone marrow samples is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected.
3. I understand that the samples will be sent along with information about me, which will include NHS number or CHI number for Scotland and may include my name.
4. I agree to these samples being stored and used for research investigations that form part of the RADAR study, and understand that this will include genetic research (for example, analysis of DNA).

- 5. I understand that a unique reference number will be allocated to the samples which may allow them to be linked back to me in future for research purposes.
- 6. I understand that my data may be shared on a collaborative basis with researchers in the UK and potentially, centres abroad.
- 7. I agree to allow any information provided to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible.
- 8. I understand that results of my laboratory tests may be shared with other research teams if I am taking part in another clinical study being run by the University of Leeds.
- 9. I agree to a copy of this Consent Form being sent to the Clinical Trials Research Unit.
- 10. I agree for my details (which will include date of birth and NHS number or CHI number for Scotland) to be submitted to NHS Digital or other central UK NHS bodies so that information about my health, and mortality should this become available, may be obtained by the CTRU if necessary.
- 11. I agree to provide bone marrow samples.

**Please indicate your wishes in the below scenarios:**

A) If I am diagnosed with a plasma cell dyscrasia, other than myeloma, I give permission for the samples sent to the central laboratories to be stored and used in future research that receives ethical approval. I understand that the samples and data collected from them may be shared with researchers, possibly in other countries.

**Please initial**

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

B) If I am diagnosed with myeloma but do not take part in the RADAR study, I give permission for the samples sent to the central laboratories to be stored and used in future research that receives ethical approval. I understand that the samples and data collected from them may be shared with researchers, possibly outside the EEA.

Yes	No
<input type="checkbox"/>	<input type="checkbox"/>

**Patient (to be completed by the patient):**

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the request to the above named patient and he/she has indicated his/her willingness for samples of bone marrow to be sent to the RADAR laboratories.

Signature.....

Name (block capitals).....

Date.....

**(If used)Translator:**

Signature.....

Name (block capitals).....

Date.....

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

For peer review only

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**Part A: Initial Treatment and Further Study Consent**

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)**

**INFORMED CONSENT DOCUMENT PART A**

**Initial Treatment and Further Study Information**

PLEASE INITIAL EACH BOX

- 12. I confirm that I have read and understand the Part A information document for the RADAR study and have had the opportunity to ask questions.
- 13. I understand that my participation in this study is voluntary and that I am free to withdraw at any time without my medical care or legal rights being affected. I understand that even if I withdraw from the above study, the data and samples collected from me will be used in analysing the results of the study, and in some cases further information about any unwanted effects of my treatment may need to be collected by the study team.
- 14. I understand that my healthcare records may be looked at by authorised individuals from the study team, regulatory bodies or Sponsor in order to check that the study is being carried out correctly.
- 15. I am aware that I am required to have samples taken and sent to laboratories and I understand that this will include genetic research (for example, analysis of DNA). I understand that the samples will be sent along with information about me, which will include NHS number, or CHI number for Scotland, and may include my name.

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16. I understand that results or reports from imaging scans, blood tests or other investigations (including for additional cancers) may be sent to the Clinical Trials Research Unit for central review by the research team.
17. I agree to allow any information or results arising from this study to be used for healthcare and/or further medical research upon the understanding that my identity will remain anonymous wherever possible.
18. I understand that my data and results of my laboratory tests (blood, urine and bone marrow sample collections) may be shared with other research teams if I am taking part in another clinical study being run by the University of Leeds.
19. I agree for my details (which will include date of birth and NHS number or CHI number for Scotland) to be submitted to NHS Digital or other central UK NHS bodies so that information about my health may be obtained by the CTRU if necessary.
20. I understand that my GP, or any other doctor treating me, will be notified of my participation in this study.
21. I understand that some of my data may be passed to other organisations, such as the pharmaceutical companies Sanofi and Celgene, (possibly in other countries where the data protection standards and laws may be different from the UK) to monitor the safety of the treatment(s) that I am receiving. I understand that my identity will remain anonymous.
22. I agree to a copy of this Consent Form being sent to the Clinical Trials Research Unit.
23. I agree to take part in the study.

**The following parts of the study are OPTIONAL (see section 3 of the Participant Information Sheet).** Even if you agree to take part in the RADAR study, you do not have to agree to these optional parts. Please initial yes or no.

Please initial

A) I agree to take part in the Quality of Life and Healthcare Resource Use studies by completing questionnaires at timepoints throughout the study.

Yes  No

B) I give permission for samples that I provide to be used in future research that receives ethical approval, and I understand that this includes the bone marrow samples provided at the time of my diagnosis (if I consented separately to collection of the diagnostic bone marrow sample in anticipation of participation in this study). I understand that my samples and data collected from them may be shared on a collaborative basis with researchers in the UK and, potentially, centres abroad.

Yes  No



**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

Date.....

(If used) Translator:

Signature.....

Name (block capitals).....

Date.....

(1 copy for patient; 1 for the CTRU; 1 held in patient notes, original stored in Investigator Site File)

For peer review only

**Part B: Randomisation 1 Treatment Group**

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)**  
**INFORMED CONSENT DOCUMENT PART B**  
**R1 Treatment Group**

PLEASE INITIAL  
EACH BOX

24. I confirm that I have read and understand the Part B information document for the RADAR study and have had the opportunity to ask questions.

25. I agree to continue my participation in the study as part of the R1 Treatment Group.

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

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9 Name (block capitals).....  
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For peer review only

**Part C: Randomisation 2 Treatment Group**

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)  
INFORMED CONSENT DOCUMENT PART C  
R2 Treatment Group**

**PLEASE INITIAL  
EACH BOX**

26.I confirm that I have read and understand the Part C information sheet for the RADAR study and have had the opportunity to ask questions.

27.I agree to continue my participation in the study as part of the R2 Treatment Group.

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

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For peer review only

**Part D: Randomisation 3 Treatment Group**

Delete this line, then print on Trust/Hospital headed paper

Participant ID:	Initials:
Date of Birth:	NHS or CHI number for Scotland/Hospital Number:
EudraCT Number:	Principal Investigator:



**RADAR (UK-MRA Myeloma XV)  
INFORMED CONSENT DOCUMENT PART D  
R3 Treatment Group**

**PLEASE INITIAL  
EACH BOX**

28. I confirm that I have read and understand the Part D information sheet for the RADAR study and have had the opportunity to ask questions.

29. I agree to continue my participation in the study as part of the R3 Treatment Group.

**Patient** (to be completed by the patient):

I agree to take part in this study.

Signature.....

Name (block capitals).....

Date.....

**Investigator:**

I have explained the study to the above named patient, and he/she has indicated his/her willingness to participate in this study.

Signature.....

Name (block capitals).....

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For peer review only

## 8 Central Sample Analysis

The trial has 3 central laboratories receiving samples for trial purposes. The time points and the reason for analysis for each central sample can be found in Figure 2. Details on the analysis of each sample is below. Note that participants can consent for their samples to be used in future research and hence each laboratory can store their trial samples for use in future studies. The storage details are also included below.

### Birmingham

The Birmingham University Clinical Immunology Laboratory holds UKAS ISO 15189:2012 - Medical Laboratories accreditation. The Trial-related Laboratory Work will be performed using standard assays to the same quality standard as during routine clinical care. The Laboratory will be responsible for the analysis of whole clotted blood, serum and urine collected from participants of the Research Project in accordance with the Protocol. The laboratory will measure disease response and Disease progression, defined according to the IMWG 2016 response criteria for Multiple Myeloma<sup>21 26-28</sup>. This will include assessment of prognostic markers, markers of disease activity and M-protein levels. Analyses will include serum levels of beta-2 microglobulin, immunoglobulins IgG, IgA and IgM, kappa and lambda free immunoglobulin light chains. Serum electrophoresis and immunofixation, M-protein quantitation including total protein and densitometry. Urine immunofixation and free light chain quantitation will be performed where appropriate. As the trial proceeds new biomarkers of myeloma disease activity are likely to become available and will also be measured. The Laboratory will ensure that the Materials are received, handled, analysed, stored and destroyed in line with the individual consent provided.

### HMDS

The presence of minimal residual disease will be assessed in bone marrow aspirates using a validated flow cytometry assay (sensitivity  $\leq 0.001\%$ ) performed at a single central laboratory (HMDS, Leeds Teaching Hospitals Trust). A minimum of 2,500,000 cells will be evaluated with an eight-colour antibody combination of CD138, CD38, CD45, CD19, CD56, CD27, CD81 and CD117. Additional antigens for detection of CD38-negative plasma cells will be utilised as required. % neoplastic plasma cells and % normal plasma cells as a percentage of leucocytes will be reported. Limit of detection (LoD) and limit of quantification (LoQ) will also be calculated for each sample. Samples will be used for trial purposes only and will not be stored for future research.



## UCL

### **Bone marrow aspirates, peripheral blood and bone marrow trephine processing within UCL Myeloma Lab for RADAR clinical trial**

#### **OBJECTIVES**

To provide molecular and genetic data on bone marrow immune profiles of newly diagnosed myeloma patients prior and post autologous stem cell transplantation. This will also be analysed between study arms to compare how different treatment regimes alert immune landscape in patients in particular anti-CD38 mAb Isatuximab.

#### **METHODS**

##### **BMA and PB:**

1. Sites are requested to collect samples and ship as per Lab Manual together with completed sample request form.
2. All samples will be processed in Myeloma Lab at UCL Cancer Institute.
3. UCL ECMC GCLP Facility will serve as storage facility for the following materials: PB plasma, BM serum, pellets (BM, PB, CD138+ and CD138-), protein lysates, extracted RNA and DNA. All material to be stored at -80°C.
4. Myeloma Lab will serve as processing facility for all samples and storing of the following materials: BM MNCs (mononuclear cells), PB MNCs, CD138+ cells and CD138- cells. All material to be stored in liquid nitrogen.
5. Both -80°C freezers and liquid nitrogen tanks are temperature monitored with systems that alert when temperature is out of acceptable range.
6. All samples and material extracted will be logged into the trial specific lab book and database with a unique trial ID, lab ID and time-point.
7. Upon arrival bone marrow aspirates and peripheral blood will be centrifuged. Serum (from BMA) and plasma (from PB) will be collected, aliquoted into 1-1.5ml aliquots and frozen at -80°C.
8. BMA and PB mononuclear cells will then be isolated and enriched using Ficoll density gradient centrifugation.
9. PB MNCs will then be frozen as pellets and/or cryopreserved.
10. Depending on the tumour burden in the BM MNCs samples will be either frozen as MNCs pellets and/or cryopreserved or tumour cells will be isolated.

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- 3 11. Tumour will be isolated via column-based MACS cell positive selection using CD138 magnetic
- 4 beads (MicroBeads).
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- 7 12. Depending on the number of cells isolated, CD138+ plasma cells will be frozen and stored as
- 8 pellets and/or protein lysates and/or cryopreserved.
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- 11 13. CD138- cells will be frozen and stored as pellets and/or cryopreserved.
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#### Bone marrow trephine:

- 15
- 16 1. Sites are requested to collect, process and ship samples as per Lab Manual together with
- 17 completed sample request form.
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- 20 2. Myeloma lab will serve as storage facility for bone marrow trephine slides.
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- 23 3. Upon arrival all samples will be logged into trial specific database with a unique trial ID, lab
- 24 ID and time-point.
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- 26 4. Upon arrival slides will be labelled and stored in the air-tight slide storage box.
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#### ANALYSIS

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- 34 1. High-dimensional flow cytometry will be used to profile immune context of patient bone
- 35 marrow mononuclear cells prior and post-transplant.
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- 37 2. Selected samples will be analysed further using transcriptomic profiling, T cell receptor (TCR)
- 38 sequencing or single cell sequencing and multiplex
- 39 immunofluorescence/immunohistochemistry on bone marrow trephine biopsies.
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3. Sun, X., et al., *Credibility of claims of subgroup effects in randomised controlled trials: systematic review*. BMJ, 2012. **344**.

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