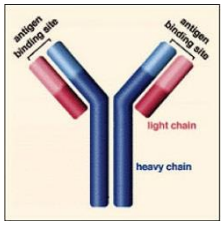


OPTIMAL

Optimising Renal outcome in Myeloma renal failure

A study of Thalidomide, Bendamustine and Dexamethasone (BTD) vs Bortezomib, Bendamustine and Dexamethasone (BBD) in patients with renal failure defined as a GFR below 30 mls/min

PROTOCOL
Version: 12.0
Date: 01 Aug 2017

EudraCT No.:	2012-003947-31
ISRCTN No.:	32505664
NCT No.:	NCT02424851
Ethics Ref No.:	13-NE-0361
Sponsor Protocol Ref.:	26866138-MMY2070
Chief Investigator:	Dr. Karthik Ramasamy
Sponsor:	Oxford University Hospitals NHS Foundation Trust
Funders:	JANSSEN-Cilag Ltd and Bloodwise (formerly named Leukaemia and lymphoma Research)

Chief Investigator Signature:

Investigator's Agreement:
I have received and read the Summary of Product Characteristics (SmPC's) for Bortezomib and Thalidomide. I have read the OPTIMAL Protocol *Version 12.0, 01 August 2017* I agree to abide by all the provisions set forth herein. The study shall be conducted in accordance with the provisions of the current version of the Declaration of Helsinki, ICH-GCP (UK 2006) and the Data Protection Act (1998). I agree to comply with all the regulations regarding clinical research that apply in the UK. I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation and conduct of the clinical investigation without the prior written consent of the Sponsor Oxford University Hospitals NHS Foundation Trust.

Name of Investigator (print):	
Signature of Investigator:	
Date:	

Confidentiality Statement

TABLE OF CONTENTS

CONTACTS:

Chief Investigator:	**Dr. Karthik Ramasamy** Consultant Haematologist Oxford University Hospitals NHS Foundation Trust, Cancer Centre Churchill Hospital Old Road Headington OX3 7LE	**Tel:** 01865 235882 **Fax:** 01865 235260 **Email:** kramasamy@nhs.net
Sponsor:	**Oxford University Hospitals NHS Foundation Trust** Research and Development Department Joint Research Office, Block 60 Churchill Hospital Oxford OX3 7LE	**Tel:** 01865 572237 **Fax:** 01865 572242
Peer review and endorsement:	**Bloodwise (formerly named Leukaemia and lymphoma Research)**	
Funders:	**Janssen-Cilag Ltd** 50-100 Holmers Far Way High Wycombe Bucks HP12 4EG	**Bloodwise** 39-40 Eagle Street London WC1R 4TH
Collaborators:	**Professor Mark Drayson** Director Clinical Immunology Service School of Immunity and Infection College of Medicine and Dentistry University of Birmingham Edgbaston, Birmingham B15 2TT	**Tel:** 01214 144074 **Fax:** 01214 143069 **Email:** m.t.drayson@bham.ac.uk
Collaborators:	**Prof Stephen Schey** Consultant Haematologist Kings College Hospital London SE5 9RS	**Tel:** 020 3299 4550 **Fax:** 020 3299 4289 **Email :** sschey@nhs.net

	Professor Janet Dunn Prof. of Clinical Trials & Head of Cancer Trials Warwick Clinical Trials Unit (WCTU) Division of Health Sciences Warwick Medical School University of Warwick Coventry, CV4 7AL	**Tel:** 02476 575847 **Fax:** 02476 528375 **Email:** j.a.dunn@warwick.ac.uk
Statistician:	**Dr Gulnaz Iqbal** Statistician Warwick Clinical Trials Unit (WCTU) Division of Health Sciences Warwick Medical School University of Warwick Coventry, CV4 7AL	**Tel:** 02476 575847 **Fax:** 02476 528375 **Email:** g.iqbal@warwick.ac.uk
Safety Data Monitoring Committee:	**Prof Kwee Yong** Department of Haematology, UCLH 1st Floor Central, 250 Euston Road, London NW1 2PG	**Tel:** 020 3447 8028 **Fax:** 020 3447 9911 **Email:** kwee.yong@ucl.ac.uk
	Dr Matthew Jenner Mailpoint 8, Level C Southampton General Hospital, Tremona Road, Southampton, SO16 6YD	**Tel:** 023 8120 4438 **Email:** Matthew.Jenner@uhs.nhs.uk
	Dr Matthew Streetly Department of Clinical Haematology 4th floor, Southwark Wing Guy's Hospital Great Maze Pond London SE1 9RT	**Tel:** 020 7188 2757 **Email:**Matthew.Streetly@gstt.nhs.uk
Trial Steering Group Chair:	**Professor Margaret Rees** 1 Hawthorn Rd West Newcastle upon Tyne Tyne and Wear NE3 4DN	
Clinical Trial Coordinator:	**Clinical Trial Coordinator** Late Phase Haematology Research Team Churchill Hospital Headington Oxford, OX3 7LE	**Tel:** 01865 223353 (Mon-Fri, 9am to 5pm) **Email:** optimal.trial@nhs.net

For general queries, drug orders, supply of trial materials, collection of data and SAE reporting please contact the OPTIMAL Trial Coordinator

Randomisation:	**Warwick Clinical Trials Unit (WCTU)** The University of Warwick Gibbet Hill Road Coventry CV4 7AL	**Tel:** 02476 150402 (Mon-Fri, 9am to 5pm) **Fax:** 02476 151586
Central Laboratory (Birmingham):	**Clinical Immunology Laboratory** University of Birmingham PO Box 1894 Vincent Drive, Edgbaston Birmingham B15 2SZ	**Tel:** 0121 414 4069 **Fax:** 0121 414 3069
Central Laboratory (Oxford):	**Molecular Haematology Lab** Level 4 John Radcliffe Hospital Headington Oxford OX3 9DU	**Tel:** 01865 220381 **Email**: maite.cabes@nhs.net
Distributer for Bortezomib	**B&C** Florence Brassart Watson & Crick Hill Rue Granbonpré, 11 B-1348 Mont-Saint-Guibert (Belgium)	**Tel:** +32 10 237 437 **Fax:** +32 10 238 850

RANDOMISATION

To randomise a participant please contact Warwick Clinical Trials Unit:

Tel: 02476 150402 (Mon-Fri, 9am to 5pm)*

Fax: 02476 151586 (Mon-Fri, 9am to 5pm)

* excluding public holidays or dates when notice has been given by the Trial Coordinator

SAE REPORTING

Please send all SAE Forms to OPTIMAL Trial Team within 24 hours of becoming aware of event:

Email: **OPTIMAL.trial@nhs.net** (Mon-Fri, 9am to 5pm)*

* excluding public holidays or dates when notice has been given by the Trial Coordinator)

1. SYNOPSIS

Background

Renal impairment is a life threatening complication of myeloma. Up to 20-25% of patients will present at myeloma diagnosis with renal dysfunction. Outcome is poor as a result of a high early mortality, with 28% of newly diagnosed myeloma patients in myeloma trials with renal failure not surviving beyond 100 days compared with 10% overall. The MERIT trial and results of studies in Mayo Clinic and Birmingham show that within weeks of diagnosing myeloma with renal failure, treatment with dexamethasone alone or combined with bortezomib lowers serum free light chain (sFLC) levels by more than 50% in half of patients. Importantly, achieving lower sFLC levels in this early period is associated with a greater chance of being alive and dialysis free at 100 days.

Aims

1) Establish whether proteasomal inhibition (bortezomib) or immunomodulatory (thalidomide) based therapy achieves threshold reduction of sFLCs in a significant majority of patients.
2) Establish whether sFLC response to the first two cycles (early responder) predict haematological and renal response to next two cycles of therapy.
3) Establish an early time point for assessment of sFLC reduction as a biomarker for response.

Methods

In this Phase II trial, 120 newly diagnosed myeloma patients with eGFR less than 30mls/min will be randomised to receive a minimum of 4 cycles of either thalidomide or bortezomib; all participants will also receive bendamustine and dexamethasone in three weekly cycles. Randomisation will be stratified based on age and Chronic Kidney Disease staging. sFLC response to the first two cycles of therapy will be used as the primary endpoint. All other endpoints are secondary. Participants will be recruited from up to 20 sites across the UK.

Retrospective analysis of 54 patients treated from 18 centres in 10 countries showed that bortezomib patients had a median sFLC reduction of 79% by day 12 compared to 66% in the thalidomide patients (35). A realistic difference between treatment arms can be detected by recruiting 60 patients in each arm. This will allow the detection of 23% differences in the percentage of patients achieving 50% reduction in sFLC between treatment arms, e.g. from 60% to 83%, with 80% power and a 5% 2-sided significance level.

Use of research results

The results of this trial will be used to show if bortezomib based induction is superior to thalidomide based induction for threshold sFLC reduction, which is important in light of NICE approval for bortezomib use upfront only in thalidomide contraindicated or intolerant patients. Early identification of poor responders based on sFLC response who may benefit from alternative therapy will be derived from this study to build a Phase III question.

Trial Title	**Opt**imising Renal outcome **i**n **M**yeloma ren**al** failure - A study of Thalidomide, Bendamustine and Dexamethasone (BTD) vs Bortezomib, Bendamustine and Dexamethasone (BBD) in patients with renal failure defined as a GFR below 30 mls/min	
Short Title	OPTIMAL	
Clinical Phase	Phase ll	
Trial Design	Randomised Control Phase II trial. Participants will be stratified by age and CKD disease stage to receive either bortezomib, bendamustine and dexamethasone (BBD) or thalidomide, bendamustine and dexamethosone (BTD)	
Trial Participants	Newly diagnosed myeloma patients with eGFR less than 30mls/min presenting with renal failure	
Planned Sample Size	120	
Treatment duration	4-6 cycles	
Follow up duration	Maximum 12 months post randomisation.	
Planned Trial Period	3 years 6 months	
	Objectives	**Outcome Measures/Endpoints**
Primary	To compare serum free light chain response to two cycles of therapy with either bortezomib (Arm A) or thalidomide (Arm B) To determine if myeloma response is associated with renal response at the end of cycle 4 (co-primary end point)	Proportion of participants with response defined as >50% reduction from baseline in sFLC at week 6 (after receiving two cycles of therapy) Renal response at end of 4 cycles of therapy. Modified IMWG Uniform Criteria Of Response and Progression 1998, 2006, 2011
Secondary	To assess whether sFLC response can predict overall response and correlation of sFLC with monoclonal protein in the urine Assess haematological and non–haematological toxicity in both treatment arms Survival Compare change in renal function at the end of cycles 2 and 4 between the two treatment regimens To evaluate treatment effects on other patient reported outcomes	sFLC response at end of weeks 1, 2, 3, 4, 5, 6, 9 and 12 of treatment with bortezomib (Arm A) or thalidomide (Arm B) Toxicity as defined by NCI CTCAE v4.0 Haematological responses Adverse Events (NCI CTCAE v4.0) Overall survival from randomisation to end of study period (assessed at 1 month post end of treatment and 12 months post randomisation) Renal response at end of second and fourth cycles of therapy as defined by IMWG renal response criteria Quality of life measured by EQ-5D (38)

Investigational Medicinal Products (IMPs)	Bortezomib Thalidomide
Non Investigational Medicinal Product (nIMPs)	Dexamethasone Bendamustine
Treatment Regimens	Four 21 day cycles (participants not suitable for ASCT will continue up to 6 cycles on the treatment regimen to which they were randomised) **Arm A (BBD)** Bortezomib: 1.3 mg/m^2 subcutaneously* days 1, 4, 8 and 11 of each cycle Bendamustine: 60 mg/m^2 i.v. days 1 and 8 of each cycle Dexamethasone: 40 mg orally days 1-2, 4-5, 8-9 and 11-12 of each cycle The cycle is repeated every 3 weeks (21 days). For cycles 3-4 (and 5-6, where relevant) bortezomib may be given as 1.3 mg/m^2 weekly for 3 weeks in a 21 day cycle in combination with bendamustine and dexamethasone. **intravenous infusion available in case of* participant *intolerance to subcutaneous bortezomib (see Section 9.3)* (Participants over 70 years of age and frail, as defined by having an ECOG score of > 1, the dose of dexamethasone will be reduced from 40 to 20 mg daily) **Arm B (BTD)** Thalidomide: 100 mg daily orally, preferably at night, days 1-21 of each cycle Bendamustine: 60 mg/m^2 i.v. days 1 and 8 of each cycle Dexamethasone: 40 mg orally days 1-2, 4-5, 8-9 and 11-12 of each cycle The cycle is repeated every 3 weeks (21 days). (Participants > 70 years of age, frail (ECOG >1) participants the dose of dexamethasone will be reduced from 40 to 20 mg daily)

2. ABBREVIATIONS

AE	Adverse event
ANC	Absolute Neutrophil Count
AP	Anteroposterior
AR	Adverse reaction
ASCT	Autologous Stem Cell Transplant
BBD	Arm A of trial treatment: Bortezomib, bendamustine and dexamethasone
BDD	Bortezomib, doxorubicin and dexamethasone
BTD	Arm B of trial treatment: Thalidomide, bendamustine and dexamethasone
CKD	Chronic Kidney Disease
CI	Chief Investigator
CR	Complete Response
CRD	Cycolphosphamide, lenalidomide and dexamethasome
CRDa	Cycolphosphamide, lenalidomide and dexamethasome; attenuated
CRF	Case Report Form
CT	Clinical Trials
CTA	Clinical Trials Authorisation
CTD	Cyclophosphamide, thalidomide and dexamethasone
CTDa	Cyclophosphamide, thalidomide and dexamethasone; attenuated
CTU	Clinical Trials Unit
DMC/DSMC	Data Monitoring Committee / Data and Safety Monitoring Committee
DoB	Date of Birth
DSUR	Development Safety Update Report
ECG	Electrocardiogram
FBC	Full blood count
FLC	Free Light Chain
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GP	General Practitioner
IB	Investigators Brochure
ICF	Informed Consent Form
ICH GCP	International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use
IMP	Investigational Medicinal Product
IMWG	International Myeloma Working Group criteria
MDRD	Modification in Diet in Renal Disease

MHRA	Medicines and Healthcare products Regulatory Agency
MR	Minor Response
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
nIMP	non-Investigational Medicinal Product
ORR	Overall Response Rate
PA	Posteroanterior
PI	Principal Investigator
PIS	Participant/ Patient Information Sheet
PR	Partial Response
PRO	Patient Reported Outcomes
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
sFLC	Serum Free Light Chain
SIV	Site Initiation Visit
SmPC	Summary of Medicinal Product Characteristics
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TSC	Trial Steering Committee
TSG	Trials Safety Group
VAD	Vincristine, Adriamycin and Dexamethasone
VGPR	Very Good Partial Response

3. BACKGROUND AND RATIONALE

Myeloma is a cancer of bone marrow plasma cells that causes 1) impaired red blood cell formation (haematopoiesis) and anaemia 2) renal failure 3) osteoporosis, lytic bone disease and skeletal fractures 4) immunosuppression and consequent infection. There are approximately 4,000 new UK cases of myeloma per annum (1) .The overall prevalence however is likely to be increasing given the recently published data demonstrating improved survival rates over the last decade (2, 3). The median age at presentation is approximately 70 years while only 15% of patients are aged less than 60 years. Myeloma has a higher incidence in Afro-Caribbean ethnic groups compared to Caucasians, but there are few other distinctive epidemiological features. The majority of cases present *de novo* but it is now recognised that this is preceded by an asymptomatic monoclonal gammopathy of undetermined significance (MGUS) phase in virtually all patients (4).

Renal impairment is a common and potentially serious complication of myeloma. Up to 20-25% of patients will present at initial diagnosis with some degree of renal dysfunction (5), and it occurs in up to 50% of patients at some time during their disease (6). It is possible to reverse renal insufficiency in approximately half of patients (7) but half will have some degree of persistent renal impairment, and of these 2-12% will require renal replacement therapy.

Renal failure occurs commonly in myeloma because of damage caused to renal tubules by free light chains, a process called cast nephropathy, or 'myeloma kidney'. The risk of renal damage is directly proportionate to the level of urinary free light chain excretion and not attributable to the light chain class or the presence or absence of whole M-proteins. Only 2% of patients without urinary free light chain excretion have renal impairment but this percentage increases to 50% with increasing levels of urinary free light chain excretion (8).

Over the past decade overall survival prospects for patients with multiple myeloma have considerably improved with projected median survivals of 6-7 years for patients in the high intensity arm of the most recent MRC trial Myeloma IX (9). However the outcome for patients with multiple myeloma complicated by renal impairment lags behind the improved results seen for patients without significant renal impairment.

This is mainly as a result of a high early death rate, with 28% of newly diagnosed myeloma patients in myeloma trials with renal failure not surviving beyond 100 days compared with 10% overall (10). It has been shown however that those surviving the first 60 days have similar overall survival to patients without renal failure.

Some progress has been made since the early 1970s when median survival was 2 months for patients with a blood urea >13 mmol/l compared to 37 months for those with a urea <6.52 mmol/l. By 1998 Torra and Blade *et al.* reported further improvements with median survival of patients with renal impairment reaching 20-24 months (11). Recent studies in 2009 reported by Kastritis *et al.* have shown that in the era of high dose steroid containing regimens, further improvements in survival have been achieved. In particular the use of high dose steroids, with or without novel agents, was shown in these studies to be associated with better rates of renal recovery and with reversal of dialysis dependency occurring in up to 40% of patients compared to rates of only 10% seen up to the 1990s (12).

It is therefore crucially important to take effective action to try and prevent renal failure, or if established, to reverse it as this will significantly improve long term prognosis (13).

MERIT (MyEloma Renal Impairment Trial) is a randomised controlled trial of adjunctive plasma exchange in patients with newly diagnosed multiple myeloma and acute renal failure from the Renal Association and the UK Myeloma Forum. In MERIT's first 59 patients with newly diagnosed myeloma and serum creatinine >500µmol/L:-

- Median reduction in malignant serum free light chain (sFLC) levels by 2 weeks (usually 5 days) of dexamethasone alone (40 mg days 1-4 & 9-12) was: 69% (range: -78% to +99%);
- This reduction was greater in the patients who were alive and independent of dialysis at 100 days (median 76.5% versus 53.2% reduction).
- The 18 patients who were alive and dialysis independent at 100 days had lower sFLC levels (*P*=0.019) than the 34 patients who were dialysis dependent and the 7 who died

It follows from the MERIT results that in treating patients with myeloma and renal impairment, regimens which give the greatest depth and speed of response should be chosen so that light chain production is reduced to the lowest level possible and as fast as possible. To ensure greatest tumour kill such regimens should be able to be given without significant dose reduction in this setting. They should be well tolerated with as few side effects as possible given the vulnerability of this patient group who often face problems with infection, fluid balance and metabolic issues.

It has been shown that high dose steroid containing regimens are effective in rapidly killing myeloma cells and can safely be given without dose reduction in renal impairment (14). Analysis of sFLC responses in MERIT shows that this happens very quickly, mostly within 5 days in responding patients (15).

However, the addition of an alkylator and a novel agent to high dose steroids will increase both the rate of response and also the proportion of patients achieving complete responses or very good partial responses.

Bendamustine (γ-[1-methyl-5-bis(β-chloroethyl) -amino-benzimidazolyl-2]-butyric acid hydrochloride) has dual mechanism of action as an alkylating agent and antimetabolite (16). Bendamustine exhibits partial cross resistance to other alkylating agents and is effective in patients with relapsed myeloma. Bendamustine is metabolised to hydroxyl derivatives with rapid elimination by hepatic and renal excretion. Pharmacokinetic data available in myeloma patients with renal impairment shows no accumulation of drug in patients with end stage renal disease. Metabolites were present in the dialysate and only 5% of the administered dose detected in the urine (17). Up to 20% of administered bendamustine is renally eliminated within 24 hours of dosing, making this drug a potential therapeutic option for patients with renal impairment.

The mechanism of action of bendamustine is through promoting myeloma cell apoptosis and cell cycle arrest. Caspase 3 activation is seen in myeloma cell lines treated with bendamustine, this would enhance synergy with other agents such as dexamethasone and thalidomide used in myeloma. Cell cycle arrest in G2 phase is through inhibition of ATM and Chk2 and not ATR and CHk1, which markedly contrasts the mechanism of action in comparison to traditional alkylating agents (18). A phase III randomised trial was performed comparing bendamustine and prednisolone (BP, bendamustine dose 50 mg/m^2 days 1-2 every cycle) with, the gold standard for myeloma, melphalan and prednisolone (MP). Although the overall response rate was comparable between 75% in the BP and 70% in the MP group, a significantly higher number of patients treated with BP achieved a complete remission than did patients receiving MP (32 vs. 13%; *P*=0.007). A critical observation was, maximum response was achieved more rapidly in patients treated with BP compared to MP (6.8 vs. 8.7 cycles; *P*<0.02). Haematological toxicities were comparable between both groups (19). A dose escalation study of single agent bendamustine in 31 heavily pretreated myeloma patients (all were post autograft), confirmed efficacy and safety of this agent. Only one episode of febrile neutropaenia was observed at the maximum tolerated dose (MTD) of 100 mg/m^2 (20).

Melphalan is less suitable in renal failure as the manufacturer recommends that initial doses of melphalan should be reduced by 50% if the glomerular filtration rate (GFR) is <40-50 ml/min, and that melphalan should not be used in patients where the GFR is below 30 ml/min. Renal dosing of cyclophosphamide remains controversial. Cyclophosphamide pharmacokinetics assessed in groups of patients with CKD stages 3, 4 and 5 after intravenous doses of 0.5 – 1 g/m^2 showed significant reduction in clearance. Cyclophosphamide is dialysable which enhances clearance in Chronic Kidney Disease (CKD) stage 5 patients (21). The manufacturer says consistent advice about dosing in poor renal function cannot be given with available data.

Thalidomide pharmacokinetics seem to be unaltered in patients with renal dysfunction (22). Less than 1% of thalidomide is excreted unchanged in the urine and it does not appear to be hepatically or renal metabolised to any large extent, appearing to undergo non-enzymatic hydrolysis in plasma to form multiple degradation products, which may be metabolically active. Manufacturers do not recommend dosage reduction, but caution in renal impairment is recommended. Although the clearance of thalidomide is increased during dialysis it appears not necessary to give a supplementary dose. A report of thalidomide use in 20 patients with renal impairment did not show any increase in toxicity (23). Extensive clinical experience has been gained with thalidomide in myeloma patients with renal impairment, with no added toxicity.

Thalidomide, alkylator and steroid containing regimens have been shown to be associated with a high rate of complete response (CR) and very good partial response (VGPR) varying from 23 - 47% in patients with myeloma. In MRC Myeloma IX Trial 555 patients received cyclophosphamide, thalidomide and dexamethasone (CTD) induction therapy giving 82.5% CR+VGPR+PR rates and 426 older patients received CTD attenuated (CTDa, dexamethasone reduced from 40 mg to 20 mg) giving 63.8% CR+VGPR+partial response (PR) rates(9, 24)**.** sFLC response was not measured at early time intervals in Myeloma IX but it is expected that the responses were at least as good as for dexamethasone alone. Retrospective study in a select cohort of myeloma patients with CKD 4 and CKD 5 confirmed the safety of the combination of bendamustine (120 mg fixed dose), thalidomide and dexamethasone in this population. It was also observed that three out of four patients who were dialysis dependent became dialysis independent after therapy (25). Grade 3-4 neutropaenia was observed in 1/9 patients. This formed the rationale for investigating the efficacy of this combination in a larger cohort of myeloma patients (MUK one trial ISRCTN90889843). This trial will also identify the right dose of bendamustine in myeloma patients in combination with thalidomide and dexamethasone, including patients with a creatinine clearance of up to ≥10 ml/min.

Bortezomib has been shown in *in vitro* studies to be metabolised primarily through oxidative deboronation by the liver cytochrome P450 system. Early disposition kinetics of bortezomib in patients did not appear to be affected by creatinine clearance (range <30 ml/min to >80 ml/min) (bortezomib SPC).

A number of studies have shown that bortezomib, either alone, or in combination with other agents, produces similar response rates in patients with renal impairment to patients with normal renal function, and can be safely delivered with no excess toxicity. These include sub-analyses of patients with renal impairment in the SUMMIT, CREST and APEX studies (26, 27). Importantly bortezomib was shown to produce rapid response rates with time to first response being 1.4 months in patients receiving bortezomib, melphalan and prednisolone in the VISTA study compared to 3.5 months in those receiving melphalan and prednisolone alone (28). This has now become standard of care for elderly myeloma patients.

Bendamustine and bortezomib in combination with steroids have been used both in newly diagnosed myeloma patients with renal impairment and in relapsed refractory myeloma patients. In the renal study,

bendamustine dosing of 60 mg/m^2 days 1 and 2 in combination with bortezomib was well tolerated with best biochemical response reached in 11/18 patients by the end of 2 cycles of therapy (29). Berenson *et al.* performed a Phase I/II dose finding study of bendamustine in combination with bortezomib in 44 relapsed/refractory patients and have not reached an MTD at 90 mg/m^2 dose of bendamustine (30). Berdeja *et al*. performed a Phase II study of combination of bendamustine and bortezomib and dexamethasone in newly diagnosed patients with a fixed dose of bendamustine at 80 mg/m^2 on days 1 and 4 (31). During a planned interim analysis of 18 patients, this combination produced a high overall response rate (ORR) and the majority of non-haematological toxicity was considered to be bortezomib induced. They have now switched to weekly bortezomib scheduling and are accruing more patients in this study. Ludwig *et al.* have explored the combination of bendamustine with bortezomib in the relapsed refractory setting (32). Bendamustine administered at dose between 70 mg/m^2 and 90 mg/m^2 in combination with bortezomib was well tolerated with an overall response rate of 50% in this heavily pre-treated group of patients. The German investigators have previously investigated bendamustine combinational therapy in a sequential escalation study starting with bortezomib monotherapy and addition of dexamethasone followed by bendamustine (50 – 100 mg/m^2) in non-responding patients. A total of 50 patients were evaluated with 7 patients requiring the bortezomib, dexamethasone, bendamustine (BBD) combination of which 6/7 achieved minor response (MR) or better, confirming the significant activity of this combination. Adverse effects were comparable between the three groups of patients (33). Only one patient in the BBD combination developed Grade 3-4 neutropaenia. These studies confirm the safety and efficacy of the combination of bortezomib, bendamustine and dexamethasone in myeloma patients.

In summary

The MERIT trial has shown that within two weeks of diagnosing myeloma with renal failure, dexamethasone alone can lower serum free light chain levels by more than 50% in more than half of patients. MERIT shows patients who are alive and dialysis free at 100 days (as compared to those dead or on dialysis) have lower levels of FLC at entry and greater reductions in free light chains in the first two weeks. Samples for FLC levels were obtained at 0, 5, 10, 16 & 100 days – only assessing response to 2 weeks dexamethasone (+/- plasma exchange) and not to subsequent cycles of chemotherapy, except for the much later 100 day sample.

Thus MERIT does not provide evidence on how much subsequent FLC response there was to successive cycles of chemotherapy, correlated with renal recovery or how a 2 week FLC response to dexamethasone could predict subsequent FLC response to subsequent cycles of Vincristine, Adriamycin, Dexamethasone (VAD).

OPTIMAL can answer these questions by examining individual patient FLC responses at **1, 2, 3, 4, 5, 6, 9, and 12 weeks**.

In MERIT median reduction in malignant serum free light chain (sFLC) levels by 2 weeks of dexamethasone alone (40 mg days 1-4 & 9-12; total 320 mg/cycle) was: 69% (range: -78% to +99%). In MRC Myeloma IX Trial 555 patients received Cyclophosphamide, Thalidomide and Dexamethasone (CTD) induction therapy giving 82.5% CR+VGPR+PR rates and 426 older patients received CTDa (dexamethasone reduced from 40 mg to 20 mg; 160 mg/cycle) giving 63.8% CR+VGPR+PR rates**.** In OPTIMAL we expect half of patients to receive only 160 mg dexamethasone/cycle. sFLC response was not measured at early time intervals in Myeloma IX. Analysis of response to the first cycle of CTDa/Cyclophosphamide, lenalidomide and dexamethasone attenuated (CRDa) (for the first 92 patients in Myeloma XI trial) shows 65% of patients achieve a 75% reduction in malignant FLC and 70% patients achieve a 50% reduction in malignant FLC. These Myeloma XI patients were not in renal failure and so the serum half-life of FLC was a few hours. In

OPTIMAL patients serum half-life of FLC will be a day or more because of reduced glomerular filtration. Accordingly the percentage of OPTIMAL patients achieving more than a 50% reduction in malignant FLC in response to first cycle of chemotherapy is expected to be significantly less than in Myeloma XI trial.

In limited numbers of patients with newly diagnosed myeloma and renal failure the addition of bortezomib to dexamethasone has achieved rapid and good serum free light chain responses and internationally, bortezomib is considered a good therapeutic option for myeloma patients with renal failure. Both BBD and BTD have been evaluated in small groups of myeloma patients demonstrating significant activity and safety (25, 29). Data for renal reversibility exists for dexamethasone, thalidomide and bortezomib. The rationale of adding an alkylator to the combination is the synergism with these agents exhibited in trials and rapid clinical responses obtained, which is critical for improving outcomes for myeloma patients with renal failure.

Thus there is rationale for comparing the effectiveness of a thalidomide, dexamethasone, and bendamustine regimen with a bortezomib, dexamethasone and bendamustine regimen on the basis that both are effective and can be given to patients even with advanced renal impairment.

We hypothesise:

1) A significant difference in achieving a reduction in sFLC levels during the first two cycles of therapy when comparing thalidomide versus bortezomib in combination with bendamustine and dexamethasone.

2) Light chain response at the end of two cycles predicts response to four cycles of therapy; allowing early identification of poor responders who may benefit from alternative therapy.

OPTIMAL can test how often poor early response to the first two cycles of randomised treatment will always be followed by poor response to two further cycles of the same therapy.

4. OBJECTIVES AND OUTCOME MEASURES/ENDPOINTS

Table 4.1: Objectives and Outcome Measures/Endpoints

	Objectives	**Outcome Measures/Endpoints**
Primary	To compare serum free light chain response to two cycles of therapy with either bortezomib (Arm A) or thalidomide (Arm B)	Proportion of participants with response defined as >50% reduction (from baseline) in sFLC at week 6 (after receiving two cycles of therapy)
	To determine if myeloma response is associated with renal response at the end of cycle 4 (co-primary end point)	Renal response at end of 4 cycles of therapy. Modified IMWG Uniform Criteria Of Response and Progression 1998, 2006, 2011
Secondary	Assess whether early sFLC response can predict overall response and correlation with monoclonal protein in the urine	sFLC response at the end of weeks 1, 2, 3, 4, 5, 6, 9, & 12 of treatment with bortezomib (Arm A) or thalidomide (Arm B)
	Assess haematological and non–haematological toxicity in both treatment arms	Toxicity as defined by (NCI CTCAE v4.0) Haematological responses Adverse Events (NCI CTCAE v4.0)
	Survival	Overall survival from randomisation to end of study period (overall survival will be assessed at 1 month post end of treatment and 12 months post randomisation)
	Compare change in renal function by the end of cycles 2 and 4 between the two treatment regimens	Renal response at end of second and fourth cycles of therapy as defined by IMWG renal response criteria
	To evaluate treatment effects on other patient reported outcomes	Quality of life measured by validated (EQ-5D-3L) questionnaire (38)

5. TRIAL DESIGN

OPTIMAL is a prospective, multicentre, open label, randomised control trial. At enrolment participants are randomised to one of two treatment groups:

Arm A: Bortezomib, Bendamustine and Dexamethasone (BBD)

Arm B: Thalidomide, Bendamustine and Dexamethasone (BTD)

The trial aims to recruit 120 participants from up to 20 sites across the UK. . Participants will be randomised to receive an average of 4 cycles of either bortezomib (Arm A) or thalidomide (Arm B); all participants will receive bendamustine and dexamethasone in three week cycles. Treatment period for participants receiving 4 cycles of therapy will be 12 weeks.

Participants not considered suitable for autologous stem cell transplant (ASCT) may be given up to a further two cycles of treatment (up to 6 cycles in total) in their respective arms. Treatment period for participants receiving additional cycles 5 and 6 will be 15 and 18 weeks respectively.

Assessments will be performed during treatment as per schedule summarized in Appendix A. These include local laboratory evaluations, concomitant medications, significant toxicity and adverse events. Central laboratory sampling will be performed at the end of each treatment cycle (weeks 1, 2, 3, 4, 5, 6, 9 and 12) for both Arm A and B. Participants undergoing additional cycles with have reduced assessments for cycles 5 and 6 with no central sampling during treatment.

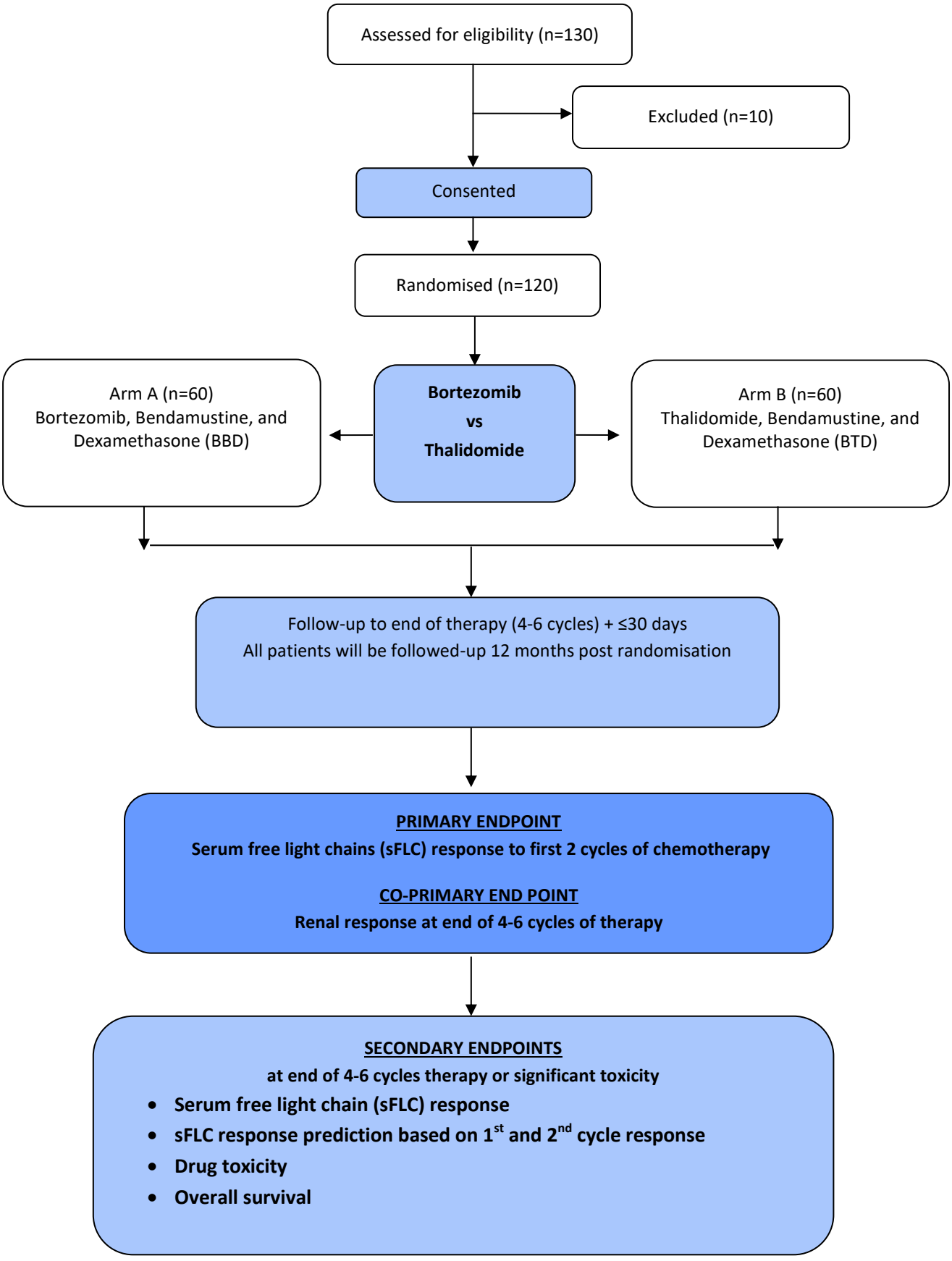
All participants who have received at least 2 cycles of treatment will be followed up. Assessments and sampling will be performed at 1 month follow-up post end of treatment (approximately 30 days after last dose). Data will then be requested at 12 months post randomisation.

Participants will also be asked to complete a validated Quality of Life Questionnaire (EQ-5D-3L) on day 1 of each treatment and at 1 month and 12 month follow up.

Any research specific assessments and sampling should coincide with routine clinical appointments wherever possible. Data will be recorded on to trial specific CRF's and entered onto a database.

See protocol section 7 and Appendix A for full details and schedule of assessment and sampling.

Figure 4.1 Trial flow diagram



6. PARTICIPANT IDENTIFICATION

6.1. Trial Participants

Patients with newly diagnosed myeloma with renal impairment defined as <30 mls/min are eligible to be included in the trial if they meet the following criteria.

6.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Male or female, aged 18 years or above.
- Patients attending NHS Haemato-oncology centres.
- Patients with newly diagnosed symptomatic myeloma.
- Glomerular Filtration Rate (GFR) <30 mls/min.
- Chronic kidney disease (CKD) staging is based on estimated or measured GFR. CKD stage 4 (15-29 ml/min) and CKD stage 5 (<15 ml/min) are eligible to enter the study. It is expected centres will consider use of fluid resuscitation and pulsed dose of steroid therapy in this group of patients to salvage renal function prior to trial screening.
- A number of patients with newly diagnosed myeloma and renal failure will have a pre-existing medical condition (hypertension, diabetes etc.) causing renal damage. Where there is a medical condition (e.g. hypertension, diabetes) which may cause renal damage, there must have been a further decline (≥15 mls/min GFR) between previous steady state and the study screening.
- Female participants of childbearing potential and male patients whose partner is a woman of childbearing potential must be willing to use contraception in accordance with (and consent to) the Celgene-approved process for thalidomide and lenalidomide Risk Management and Pregnancy Prevention Programme.
- Women of childbearing potential must have a negative pregnancy test performed by a healthcare professional in accordance with the Celgene-approved process for thalidomide and lenalidomide Risk Management and Pregnancy Prevention.
- Free of prior malignancies for $\geq$ 2 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, localised prostate cancer or carcinoma “in-situ” of the cervix or breast.
- In the Investigator’s opinion, is able and willing to comply with all trial requirements.
- Willing to allow his or her General Practitioner and consultant to be notified of participation in the trial.

6.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Female participant who is pregnant, lactating or planning pregnancy during the course of the trial or the female partner of a male participant planning a pregnancy during the course of the trial or are unwilling or unable to take sufficient precautionary measures
- Aged <18 years.
- Known allergy to investigational drugs.
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial.
- Any of the following laboratory abnormalities:
    - Absolute neutrophil count (ANC) < 1.0 x10^9/L
    - Platelet count <75 x 10^9/L
    - Serum SGOT/AST or SGPT/ALT >3 x upper limit of normal.
- Use of any standard/experimental anti-myeloma drug therapy excluding dexamethasone 14 days prior to trial entry.
- CKD stages < 4.
- Intention to use a physical method of serum free light chain removal such as plasma exchange or high cut off dialysis.
- Grade 2 neuropathy or more (NCI CTCAE v 4.0) will preclude use of thalidomide and Bortezomib.
- Participants who have participated in another research trial involving an investigational product in the past 12 weeks.
- Contraindicated to receive either one of the study drugs, thalidomide or Bortezomib, based on the respective summary of product characteristics.

Researchers will advise patients presenting with suspected myeloma and renal failure, that if they sign an OPTIMAL consent form, they will be screened for myeloma. Only once eligibility is confirmed, will they be randomised into the OPTIMAL trial.

7. TRIAL PROCEDURES

Any trial related assessments will be performed only after written informed consent is obtained. All screening study assessments must be completed before investigational product administration. The schedule of assessments is provided in Appendix A. Every effort should be made to keep participants on the study schedule as planned.

Any missed visits, or tests or assessments not completed, must be reported on the relevant CRF with the reason for the missing data. Any protocol deviations must be reported to Trial Coordinator and documented on relevant CRF.

7.1. Recruitment

Patients presenting or referred to the haematology departments at a study site with possible myeloma and renal failure will be reviewed by the site's study investigators. Potential participants will have the purpose of the trial explained to them. Written and verbal explanation of the Participant Information Sheet (PIS) will be presented to potential participants detailing no less than: the exact nature of the trial; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the trial at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal. It will be explained that there are a series of screening assessments that will be performed after consent is given (see Section 7.3), and screened potential participants may not necessarily be eligible for the trial. It

The participant will be allowed a minimum 24 hours to consider the information, and given the opportunity to discuss with the investigator, their GP or any other individuals in order to decide whether they will participate in the trial. The PIS will contain local contact details for researchers and an independent contact

7.2. Informed Consent

Each participant must personally sign and date the current approved version of the Informed Consent Form (ICF) before any trial specific procedures are performed. The correct version number and date of the PIS provided should be added to the Consent Form.

Informed consent should be obtained by the local investigator (PI). If the PI is delegating the responsibility to other suitably qualified individuals as documented on the Site Staff and Delegation Log, it remains the responsibility of the PI to ensure that the standard procedures for informed consent within a clinical trial are followed.

The local investigator is responsible for ensuring that the participants understand the risks and benefits of the trial, answering any questions the participants may have throughout the study, and sharing any new information that may be relevant to the participant's continued participation in the trial.

It is recommended that consent is taken before local bone marrow assessments, to enable trial specific bone marrow aspirate samples to be taken at the same time as standard local bone marrow samples.

As part of the consent process, participants will also be asked to gift bone marrow samples and any additional blood and urine samples for future ethically approved research. This is optional and is not required for participation in the study. These samples should only be sent if a participant has consented, and a copy of the participant Informed Consent Form included with the sample and CRF.

Participants in the study will need to consent for their data to be held in a database for research purposes, and for their information to be accessed by relevant research staff for the purposes of this trial, including OPTIMAL Coordinating Centre, Sponsor and research staff at sites. This will be detailed in the PIS and Informed Consent Form. All data will be handled according to Data Protection Act (1998) (see section 17).

Participants will be informed of their rights and ability to withdraw from the trial at any time and without giving a reason. A participant can withdraw consent fully or from specific aspects. This will be recorded using the relevant CRF. A participant can withdraw from any further sample or data collection but any samples and data already taken can still be used in data analysis. This is because samples are anonymized and so it is not possible to arrange for destruction of any existing samples or data. However, if a participant withdraws consent, no further samples or data will be collected. This will be clearly explained in the Participant Information Sheet and Consent Form.

Additionally, participants will be asked to record on the ICF whether they wish to receive a summary report of the study findings. When available the summary report will be provided by the OPTIMAL Trial Office to local study teams for dissemination to the relevant consenting participants.

The original signed Consent Form should be retained by the trial site and filed in local site file. A copy of the signed Informed Consent form should be given to the participant, and a copy of the Participant Information Sheet and Consent Form added to the participant's medical notes.

Copies of Consent Forms will also be requested by OPTIMAL Trial Coordinating Office for monitoring purposes. Consent Forms will be stored separately to any study data or other personal data and will be transferred using secure methods only.

Participants will be able to access the standard benefits locally available to all myeloma patients. No additional monetary payments as part of trial will be made.

7.3. Screening and Eligibility

7.3.1 Screening Logs

Investigators will be expected to maintain a screening log of all potential participants at their site. Participants will not be registered at consent and therefore during screening potential participants should be identified by limited information only, including Initials and Date of Birth, as well as screening date and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or refused to participate).

Screening logs will be requested from sites by the OPTIMAL Trial Team on a monthly basis. Copies of the screening logs should also be filed locally.

7.3.2 Screening Assessments

The following assessments will be carried out in order to establish eligibility for the trial.
All screening study assessments must be completed before any investigational product is administered.

The following screening procedures must be completed not more than **21 days before the day of randomisation**. In addition clinical laboratory evaluations and screening central labs samples must be taken not more than **14 days before the day of starting treatment**. Please refer to Appendix A.

- **Medical History**
  Detailed history of myeloma including; date of diagnosis, staging (**International Staging System** - - see Appendix C), and location(s) of bone disease as per standard of care. Detailed description of all prior and on-going diseases and disorders should be documented.

- **Treatment History and Concomitant Medication(s)**
  Details of treatment history and current concomitant medication including all medications, treatments and therapies used in the prior 4 weeks, as well as those currently being taken.

- **Physical Examination**
  Physical examination including assessment of ECOG performance status (refer to Appendix B for ECOG performance status), height and weight (to calculate drug dose), and baseline neuropathy.

- **Skeletal Survey/MRI**
  Skeletal survey (including spine) as per local standard of care, and MRI if clinically indicated.

- **Chest X-ray and Electrocardiogram (ECG)**
  A chest X-ray and ECG will be carried out during the screening process as per standard of care and any abnormalities recorded in the relevant CRF.

- **Local Clinical Laboratory Evaluations (**not more than **14 days before start of treatment)**
  - ***Biochemistry***: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Bicarbonate, Magnesium, Phosphate, Urea, Creatinine, LFTs, CRP, LDH, Uric acid, Glucose, Creatinine Clearance
  - ***Immunology***: Beta-2 microglobulin, sFLC, paraprotein, quantitative immunoglobulins
  - ***Haematology***: haemoglobin, haematocrit, bilirubin, WBC, platelet count, neutrophils, lymphocytes and monocytes
  - ***Bone marrow assessment***: Bone marrow aspirate and trephine to confirm diagnosis of myeloma
  - ***Urine Pregnancy Test:*** for women of child-bearing potential (WCP) (Appendix G)

- **Screening Central Laboratory Samples (**not more than **14 days before start of treatment))**
  The following samples should be collected and sent to central labs as detailed below:

  Screening Samples for Birmingham Central Labs:
  - Bone marrow aspirate 2 ml (EDTA) *
  - Blood 5 ml (EDTA)
  - Blood 10 ml (clotted)
    Urine 20 ml (universal) - for inpatients undergoing 24 hour urine collection, please collect 20 ml aliquot sample in universal container

  Screening Samples for Oxford Central Labs:
  - Bone marrow aspirate 5 ml (EDTA) *
  - Bone marrow aspirate 2 unstained slides *

**Bone marrow samples are optional gifted samples – for consenting participants only*

See Protocol Section 8 and 'Central Laboratory Sample Handling Manual' for further details on laboratory and sampling requirements and processes.

7.4 Registration and Randomisation

7.4.1 Recruitment Logs

Participants deemed eligible after screening will be registered on to the trial. Registered participants will be recorded on a recruitment log with information including Study ID, Date of Birth, Initials and hospital number as well as date of consent, date of randomisation and treatment allocation. No personal information which may identify the participant should be included on the recruitment log.

7.4.2 Randomisation

Randomisation will be performed by Warwick Clinical Trials Unit (CTU). A computer minimisation program will be used and participants will be stratified according to:

1) Age (<=70 or >70 years).

2) Chronic kidney disease (CKD) stage 4 or stage 5.

To randomize a participant, researchers should ensure they have completed both the eligibility and randomisation forms and then contact Warwick CTU by phone or alternatively fax the randomisation form on the details below:

Warwick Clinical Trials Unit

Tel: 02476 150402 (Mon-Fri, 9am to 5pm)

Fax: 02476 151586 (Mon-Fri, 9am to 5pm)

Please ensure you have completed the eligibility checklist

Participant will be randomized to either group A or group B and assigned a unique Study ID. This information will be given over the phone and/or confirmed by email. This unique Study ID will become the primary way in which the participant will be identified for the duration of the study and should be included, together with initials and date of birth, on all relevant trial documentation and correspondence.

7.4.3 Participant Trial Card

After a participant has been randomized site staff should inform the participant of their treatment allocation as soon as they are able to and provide the participant with a completed Participant Trial Card including details of their treatment allocation and local site contact details.

7.5 Treatment and Subsequent Assessments

7.5.1 Treatment: Cycles 1-4

All participants will undergo the following assessments during treatment cycles 1-4 (as per schedule, summarised in Appendix A)**:**

Day 1 of Cycles 1-4:

- **Physical Examination**
  Weight and assessment of ECOG performance status (see Appendix B)

- **Concomitant Medication**
  Details of current concomitant medication including all medications, treatments and therapies will be collected throughout treatment cycle from day 1 and recorded on the relevant CRF. This includes any changes since previous trial visit.

- **Quality of Life Questionnaire**
  Participants will be asked to complete a validated Quality of Life Questionnaire (EQ-5D-3L) (see Appendix E) on day 1 of each cycle administered

- **Local Clinical Laboratory evaluations** (see Appendix A)
    - ***Biochemistry***: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Bicarbonate, Magnesium, Phosphate, Urea, Creatinine, LFTs, CRP, LDH, Uric acid, Glucose, Creatinine Clearance
    - ***Immunology***: Beta-2 microglobulin, sFLC, paraprotein, quantitative immunoglobulins
    - ***Haematology***: haemoglobin, haematocrit, bilirubin, WBC, platelet count, neutrophils, lymphocytes and monocytes
    - ***Urine pregnancy test*****:** For women of child-bearing potential (see Appendix G for a definition). To be carried out either the day before, or on day 1 of each cycle of treatment.

- **Parenteral Drugs administered at local hospital**
  Bortezomib (Arm A only) - days 1, 4, 8 and 11 of each cycle
  Bendamustine (Arm A and B) – days 1 and 8 of each cycle

- **Drug Dispensing and Treatment Diary Card(s)**
  Dexamethasone (Arm A and B) and thalidomide (Arm B) dispensed to participants
  Participants given relevant Participant Treatment Diary Card(s) for completion

- **Adverse Event Reporting**
  Details of Adverse Events will be collected throughout treatment cycle and recorded on relevant CRF. This includes any changes since previous trial visit.

During Treatment Cycles 1-4:

- **Concomitant Medications**

  Any changes in concomitant medication including all medications, treatments and therapies will be collected throughout treatment cycle and recorded at end of cycle on the relevant CRF.

- **Central Samples (Birmingham)** will be collected to monitor changes in serum and urine paraprotein, sFLC levels and renal function **at the <u>end</u> of *weeks 1, 2, 3, 4, 5, 6, 9 and 12***
    - Blood in EDTA 5ml
    - Blood clotted 10ml
    - Urine sample 20ml in universal container - for inpatients undergoing 24 hour urine collection, please collect 20 ml aliquot sample in universal container

- **Parenteral Drugs administered at local hospital**
  Bortezomib (Arm A only) - days 1, 4, 8 and 11 of each cycle
  Bendamustine (Arm A and B) – days 1 and 8 of each cycle

- **Adverse Event Reporting**

  Details of any Adverse Events should be collected throughout treatment cycle and recorded at the end of cycle on relevant CRF. This includes follow up information for previous Adverse Events.

Samples should be sent in packaging provided together with a completed Birmingham Sample CRF form to**:**
Clinical Immunology Service, PO Box 1894, Vincent Drive, Edgbaston, Birmingham, B15 2SZ

See Protocol section 8 and 'Central Laboratory Sample Handling Manual' for further details on laboratory and sampling requirements and processes.

End of Cycles of 1-4:

- **Concomitant Medications**
  Any changes in concomitant medication including all medications, treatments and therapies will be collected throughout treatment cycle and recorded at end of cycle on the relevant CRF.
- **Drug Accountability and Collection of Treatment Diary Card(s)**
  Collection of completed Participant Treatment Diary Card(s) for dexamethasone (Arms A and B) and thalidomide (Arm B)
- **Adverse Event Reporting**
  Details of any Adverse Events should be collected throughout treatment cycle and recorded on relevant CRF. This includes follow up information for previous Adverse Events.
- **Survival**
- **Completion of Treatment Form CRF**

7.5.2 Treatment: Cycles 5 and 6

Responding participants not considered suitable for autologous stem cell transplant (ASCT) may be given up to two further cycles of treatment in their respective arms. Participants receiving additional cycles will undergo the following reduced assessments (see Appendix A):

Day 1 Cycles 5-6

- **Physical examination**
  Weight assessment of ECOG performance status (see Appendix B)
- **Concomitant medication**
  Details of current concomitant medication including all medications, treatments and therapies will be collected throughout treatment cycle from day 1 and recorded on the relevant CRF. This includes any changes since previous trial visit.
- **Quality of Life Questionnaire**
  Participants will be asked to complete a validated Quality of Life Questionnaire (EQ-5D-3L) (see Appendix E) on day 1 of each cycle administered
- **Local Clinical Laboratory evaluations** (see Appendix A)
  - ***Biochemistry***: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Bicarbonate, Magnesium, Phosphate, Urea, Creatinine, LFTs, CRP, LDH, Uric acid, Glucose, Creatinine Clearance
  - ***Immunology***: Beta-2 microglobulin, sFLC, paraprotein, quantitative immunoglobulins
  - ***Haematology***: haemoglobin, haematocrit, bilirubin, WBC, platelet count, neutrophils, lymphocytes and monocytes
  - ***Urine pregnancy test*:** For women of child-bearing potential (WCP) (see Appendix G for definition). To be carried out either day before, or on day 1 of each cycle of treatment.
- **Parenteral Drugs administered at local hospital**
  Bortezomib (Arm A only) - days 1, 4, 8 and 11 of each cycle
  Bendamustine (Arm A and B) - days 1 and 8 of each cycle
- **Drug Dispensing and Treatment Diary Card(s)**
  Dexamethasone (Arm A and B) and thalidomide (Arm B) dispensed to participants
  Participants to be given relevant Participant Treatment Diary Card(s) for completion
- **Adverse Event Reporting**
  Details of Adverse Events will be collected throughout treatment cycle and recorded on relevant CRF. This includes any changes since previous trial visit.

During Treatment Cycles 5-6

- **Concomitant Medications**
  Any changes in concomitant medication including all medications, treatments and therapies will be collected throughout treatment cycle and recorded at end of cycle on the relevant CRF.
- **Parenteral Drugs administered at local hospital**
  Bortezomib (Arm A only) - days 1, 4, 8 and 11 of each cycle
  Bendamustine (Arm A and B) - days 1, 4, 8 and 11 of each cycle
- **Adverse Events Reporting**
  Details of any Adverse Events should be collected throughout treatment cycle and recorded at the end of cycle on relevant CRF. This includes follow up information for previous Adverse Events.

End of Cycles 5-6

- **Concomitant Medications**
  Any changes in concomitant medication including all medications, treatments and therapies will be collected throughout treatment cycle and recorded at end of cycle on the relevant CRF.
- **Drug Accountability and Collection of Treatment Diary Card(s)**
  Collection of completed Participant Treatment Diary Card(s) for dexamethasone (Arms A and B) and thalidomide (Arm B)
- **Adverse Event Reporting**
  Details of any Adverse Events should be collected throughout treatment cycle and recorded on relevant CRF. This includes follow up information for previous Adverse Events.
- **Survival**
- **Completion of Treatment Form CRF**

Please note: NO Central Laboratory Samples required for participants undergoing treatment cycles 5-6.

7.6 1 Month Follow-up post Treatment

All participants completing at least 2 cycles of treatment will undergo the following assessments approximately **30 days after the final treatment or discontinuation of treatment (Appendix A)**:

- **Physical examination**
  Weight and assessment of ECOG performance status (see Appendix B)
- **Drug Accountability and Collection of Treatment Diary Card(s)**
  Collection of completed Participant Treatment Diary Card(s) for dexamethasone (Arm A and B) and thalidomide (Arm B) for last cycle of treatment
- **Local Clinical Laboratory Evaluations**
  - ***Biochemistry***: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Bicarbonate, Magnesium, Phosphate, Urea, Creatinine, LFTs, CRP, LDH, Uric acid, Glucose, Creatinine Clearance
  - ***Immunology***: Beta-2 microglobulin, sFLC, paraprotein, quantitative immunoglobulins
  - ***Haematology***: haemoglobin, haematocrit, bilirubin, WBC, platelet count, neutrophils, lymphocytes and monocytes
  - ***Bone marrow assessment***: Bone marrow aspirate and trephine for response assessments
  - ***Urine pregnancy test***: For women of child-bearing potential (WCP) (for definition of WCP see Appendix G) this final test should be performed 30 days after last dose of study drug

- **Central Laboratory Samples (Birmingham)**
    - Bone marrow aspirate 2 ml (EDTA) *
    - Blood 5 ml (EDTA)
    - Blood 10 ml (clotted)
    - Urine 20 ml (universal) - for inpatients undergoing 24 hour urine collection, please collect 20 ml aliquot sample in universal container
- **Central Laboratory Samples (Oxford)**
    - Bone marrow aspirate 5 ml (EDTA) *
    - Bone marrow aspirate 2 unstained slides *

**Bone marrow sample are optional gifted samples – for consenting participants only*

- **Quality of Life Questionnaire**
  Participants will be asked to complete a validated Quality of Life Questionnaire (EQ-5D-3L) (Appendix E)
- **Adverse Events Reporting**
  Details of any Adverse Events since end of last treatment cycle should be recorded on relevant CRF. This includes follow up information for any previous Adverse Events.
- **Treatment Efficacy Information**
  Assessment Response and Disease Progression: Serum paraprotein, serum FLCs, renal response and overall response will be assessed using International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma (36, 37) (See Appendix D) . Details on immunofixation and imaging (if clinically required).
- **Survival**

See Protocol section 8 and 'Central Laboratory Sample Handling Manual' for further details on laboratory and sampling requirements and processes.

7.7 12 Month Follow-up post Randomisation

Participants will undergo the following assessments approximately 12 months after randomisation (see Appendix A):

- **Physical examination** - Weight and assessment of ECOG performance status (see Appendix B)
- **Disease status**
- **Local Clinical Laboratory Evaluations**
    - ***Biochemistry***: Creatinine Clearance, eGFR only
- **Clinical assessment**
- **Adverse Events Reporting -** Details of any Adverse Events since last follow up visit should be recorded on relevant CRF. This includes follow up information for any previous Adverse Events.
- **Summary of Treatment -** Including hospital admission history since end of trial treatment and subsequent anti-myeloma treatment
- **Survival**

If participant is unable or unwilling to attend clinical appointment, 12 month follow up can be completed using hospital notes, if participant has given consent.

7.8. Withdrawal or Change of Status of Participants

7.8.1 Withdrawal

Participants have the right to withdraw from any aspect of the trial at any time and without giving a reason. In addition, the Investigator may withdraw a participant from some or all aspects of the trial at any time if the Investigator considers it necessary for any reason including:

- **Pregnancy –** In the case of pregnancy in a female participant the participant **must** be withdrawn from trial treatment immediately (pregnancy is an exclusion criteria), and participant should remain on-study for follow-up, unless the participant or clinician specifically requests otherwise. **Any** pregnancy in female participants or female partners of male participants should be reported to the OPTIMAL Trial Office using **SAE Reporting Form** as an "other medically important event" and **CRF Pregnancy Form A** within **24 hours of awareness**. Consent to follow-up of the pregnancy should be sought, and the outcome of the pregnancy reported to OPTIMAL Trial Office using **CRF Pregnancy Form B**. (See protocol Section 10 for further details of Safety Reporting).
- **Physical clearance of free light chains** - Participants undergoing either plasma exchange or high cut off dialysis **must** be withdrawn from study.
- **Ineligibility** either arising during the trial, or retrospectively after becoming aware of ineligibility
- **Significant protocol deviation**
- **Significant non-compliance** with treatment regimen or trial requirements.
- **Significant toxicity**
- **Adverse event** which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures.
- **Disease progression** which requires discontinuation of the trial medication or results in inability to continue to comply with trial procedures.
- **Withdrawal of consent**
- **Loss to follow up**

Withdrawal can be from all aspects of the trial or from certain aspects only. For example, it may be necessary for a participant to discontinue with trial treatment but every effort should be made to keep participants on-study for follow-up and central laboratory sampling as per protocol, unless a participant or clinician explicitly requests otherwise.

Sites should discuss any Withdrawals with Chief Investigator via OPTIMAL Trial Office prior to withdrawing a participant.

After withdrawal has been discussed with the Chief Investigator, any change in status or withdrawal should be documented on the relevant Withdrawal CRF including reason(s) for withdrawal, and which specific aspects of the trial the participant is being withdrawn from. Details of withdrawal should also be documented in the participant's hospital notes.

If a participant or clinician withdraws consent for further sampling, this should be recorded on the OPTIMAL Withdrawal Form and the OPTIMAL Trial Coordinator should be notified that no further samples will be taken for that participant. Sites must ensure all local staff are informed that no further sampling should be undertaken.

If further sampling is not possible but consent has not specifically been withdrawn e.g. participant moves to palliative or residential care, this does not need to be recorded as a withdrawal but sites should notify the OPTIMAL Trial Coordinator that no further samples will be collected and note on relevant CRF's.

Sites should ensure all local site staff are informed of any withdrawals or change of status to ensure that no further sampling or follow up is undertaken for participants who have withdrawn consent.

If a participant is withdrawn from further treatment but has completed at least 2 treatment cycles , the participant should be followed-up at approximately 30 days after their final treatment (as per the 1 month follow-up post treatment (see Section 7.6.) and at 12 months post-randomisation (see Section 7.7), unless the participant or clinician specifically requests otherwise.

If a participant is withdrawn due to an adverse event, the Investigator should arrange for follow-up visits or telephone calls to take place until the adverse event has resolved or stabilised.

Due to the sampling process and anonymising of data, it is not possible for participants to request that existing data or samples are destroyed and any existing data can be included in study analysis. However, if a participant withdraws consent, no further samples or data will be collected.

7.8.2 Loss to Follow Up

Every effort should be made to continue participant follow up as per protocol and ensure participant contact details are updated as required. If a participant is unable to be contacted for an extended period of time and follow-up not able to be completed, this should be recorded on the Withdrawal CRF as 'Loss to Follow up'. It should also be documented in the participant's hospital notes.

7.8.3 Participant Transfer

For participants moving from the area, every effort should be made for the participant to be followed-up at another participating trial site and for this trial site to take over responsibility for the participant. If the participant is happy to transfer to another site and continue follow up, the main trial contact at the current hospital should liaise with the OPTIMAL Trial Coordinator to identify a suitable receiving hospital (if possible) and facilitate the transfer. (participant names must be removed from any documentation).

The contact at the current hospital should complete a Participant Transfer form and send to the OPTIMAL Trial Office prior to the participant transfer. Any data queries for the participant should be completed prior to transfer if possible. Copies of any relevant trial documentation including Informed Consent Form must be sent to the new hospital to complete the transfer and copies must be also retained at the original site for monitoring purposes.

7.9 Definition of End of Trial

The end of trial will be the date of the last 12 month follow-up visit of the last participant.
All pregnancies during trial period will be followed to completion, if participant has given consent.

8. LABORATORY AND SAMPLING

8.1 Local Clinical Laboratory Evaluations

The following routine local clinical laboratory evaluations will be performed as per schedule (Appendix A) and the data and results used for the purposes of this trial:

- ***Biochemistry***: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Bicarbonate, Magnesium, Phosphate, Urea, Creatinine, LFTs, CRP, LDH, Uric acid, Glucose, Creatinine Clearance (Creatinine clearance in ml/min to be measured based on the following abbreviated MDRD equation : 186 x (Creat / 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black) using creatinine micromol/L. The calculator for this can be found at http://www.renal.org/egfrcalc/)
- ***Immunology***: Beta-2 microglobulin, sFLC, paraprotein, quantitative immunoglobulins
- ***Haematology***: haemoglobin, haematocrit, bilirubin, WBC, platelet count, neutrophils, lymphocytes and monocytes
- ***Bone marrow assessment***: Bone marrow aspirate and trephine to confirm diagnosis of myeloma and renal response
- ***Urine pregnancy testing***: For women of child-bearing potential (WCP) (see appendix G for definition) at screening, and again on the day of, or the day before, day 1 of each cycle. Final test should be done approximately 30 days after the last dose of study drug.

8.2 Central Laboratory Samples

The following research specific clinical laboratory evaluations should be performed as per schedule (see Appendix A and table 8.1).

8.2.1 Central Laboratory Samples (Birmingham):

- Bone marrow aspirate (2ml EDTA) at screening, and 1 month post end of treatment (or discontinuation of treatment) *
- Blood and urine for central laboratory analysis of quantitative immunoglobulins, Beta-2 microglobulin, free light chains, immunofixation of serum and urine, paraprotein quantitation by densitometry at screening, at the end of weeks 1, 2, 3, 4, 5, 6, 9, & 12 of treatment and 1 month post end of treatment (or discontinuation of treatment);
  - Blood 5 ml (EDTA)
  - Blood 10 ml (clotted)
  - Urine 20 ml in universal container - for inpatients undergoing 24 hour urine collection, please collect 20 ml aliquot sample in universal container

**Bone marrow samples are additional gifted samples – for consenting participants only. Local bone marrow assessments will be used to confirm diagnosis at screening.*

Blood and urine samples will be used in analysis of sFLC and renal response for primary and secondary endpoints. Blood samples will be analysed to try and compare the rate of production and removal of light chains between treatments, which may help to guide treatment decisions. Urine samples will be used for the assessment of sFLC, paraprotein and immunoglobulins, and for measuring renal response using IMW consensus criteria.

All samples should be accompanied by a Birmingham Central Sample CRF with a copy of the participant's Informed Consent Form.

Boxes/packaging will be sent to each site following site initiation. Please be aware that postage is not pre-paid. Samples should be sent first class post on the day of collection to the following address:

Clinical Immunology Service, PO Box 1894,

Vincent Drive, Edgbaston, Birmingham, B15 2SZ

Fax: (0)121 414 3069

Please include copies of completed Birmingham Sample CRF and signed participant Informed Consent Form

Please refer to the "**Central Laboratory Sample Handling Manual**" for further details on preparation, logging and postage of Central Laboratory samples

8.2.1.1 Sampling timing

Samples should to be taken **as close as possible** to the end of the week (day 7 of each week) +/- 2 days is acceptable i.e. if end of treatment week 1 falls on a Sunday (day 7 of week 1), blood and urine samples may be taken on the previous Friday (day 5 of week 1) or following Monday or Tuesday (days 1 or 2 of week 2).

If a participant's treatment is delayed please keep to the specified sampling time-points calculating sampling from the start of treatment, and add in additional sample collections to cover all required time-points. For example, if cycle 3 is delayed- take blood and urine samples at week 9 and 12 post start of treatment (regardless of where the participant is in their treatment schedule) and add in additional samples at the end of week 3 of cycle 3 and the end of week 3 of cycle 4. These should be recorded as "other" with details in the relevant sample CRF.

If an on-treatment sample is missed, **do not wait** until the next time-point; **take the missed sample as soon as possible** and record the time-point (as 'other' with details) on the CRF (immunology sample analysis request form).

8.2.2 Central Laboratory Samples (Oxford)

Bone marrow aspirate at screening and 1 month follow-up post end of treatment (or discontinuation of treatment):

- Bone marrow aspirate 5 ml (EDTA) *
- Two unstained slides of bone marrow aspirate. *

**Bone marrow samples are additional gifted samples – for consenting participants only.*

All samples should be accompanied by an Oxford Central Sample CRF **and** a copy of the participant's consent form. Consent Forms can be sent either by post or secured email using details below. If Consent Form is sent via post it must be sent separately to any trial data or documentation such as CRF.

Boxes/packaging will be send to each site following site initiation. Please be aware that postage is not pre-paid. Samples should be sent first class post on the day of collection. Please do not post bone marrow aspirate samples to Oxford on a Friday. If collection of bone marrow aspirate samples on a Friday is unavoidable, please refrigerate samples over the weekend and post on the following Monday.

Samples should be sent first class post on the day of collection to the following address:

FAO Molecular Haematology Lab (OPTIMAL Trial)
Level 4, Academic Centre
John Radcliffe Hospital, Headley Way, Headington, Oxford,
OX3 9DU
Email: maite.cabes@nhs.net

Please ensure you enclose copy of the Oxford Central Sample CRF **and a copy of the participant's consent form**

Please refer to the "**Central Laboratory Sample Handling Manual**" for further details on preparation, logging and postage of central laboratory samples

Table 8.1 summarising sampling requirements at time points during study.

	Screening / 1 month FU	Treatment (each cycle)	Documents	Address
BIRMINGHAM	Bone marrow aspirate EDTA (2ml) Blood EDTA 5ml Blood (clotted) 10ml Urine container 20ml	Blood EDTA 5ml Blood (clotted) 10ml Urine container 20ml	Birmingham Central Sample Form (CRF 19) Copy of Consent Form required	*Send to:* Clinical Immunology Service PO Box 1894 Vincent Drive Edgbaston, Birmingham B15 2SZ
OXFORD	Bone marrow aspirate EDTA (5ml) 2 x slides unstained bone marrow (slide box)	----------	Oxford Central Sample Form (CRF 18) Copy of Consent Form required	*Send to:* FAO Maite Cabes Molecular Haematology Lab Level 4, John Radcliffe Hospital Headley Way, Headington Oxford, OX3 9DU

8.2.3 Notifying Trial Office of Samples

Please notify OPTIMAL Trial Office when samples are collected and sent using the contact details below:

Notifying OPTIMAL Trial Office of Samples

Please notify OPTIMAL Trial Office when samples are collected and sent by sending OPTIMAL "Notification of Samples Form"

Email: OPTIMAL.trial@nhs.net

8.3 Additional gifted samples

Bone marrow samples will be collected and sent to Central Laboratories in Oxford and Birmingham to be stored for future ethically approved research, if participant has consented. Participants will also be asked to consent for any remaining serum and urine samples obtained for this trial to be stored indefinitely and used for future ethically approved research. Future research may include assessing percentage of myeloma

cells before treatment and at the end of treatment, including Minimum Residual Disease, morphology and MM FISH, and assessment of chromosomal and molecular difference before and after treatment

For additional gifted samples stored at Oxford Central Laboratory, the CI will be responsible for the custodial arrangements. For additional gifted samples stored at Birmingham Central Laboratory, the Director Clinical Immunology Service will be responsible for the analysis of these samples and the storage of any remaining non-cellular samples at the end of the study.

8.4 Availability and prioritisation of samples

Central laboratory samples should be taken at the same time as routine local samples wherever possible. If this is not possible or there is insufficient sample, local samples should be prioritised and researchers should confirm with the participant and treating clinician that an additional research sample can be taken.

It is recommended that during screening consent is taken before local bone marrow assessments, to enable trial specific bone marrow aspirate samples to be taken at the same time as standard local bone marrow samples.

Research specific blood and urine samples should be prioritised research samples as these are required for primary and secondary endpoints. Bone marrow samples are additional gifted samples although every effort should be made to obtain these if possible, for consenting participants.

9. INVESTIGATIONAL MEDICINAL PRODUCTS (IMPs)

Bortezomib and thalidomide will be considered Investigational Medicinal Products (IMPs) in this trial. Bendamustine and dexamethasone will be considered non-Investigational Medicinal Products (nIMPs) in this trial

Prior to Site Initiation Visit (SIV) each PI will be required to sign confirming their Trust's compliance with the standard thalidomide Celgene pregnancy prevention programme.

9.1 Trial Treatments

Participants will be randomised to receive one of two treatment schedules:

Arm A

Bortezomib, Bendamustine and Dexamethasone (BBD)

Participants > 70 years of age the dose of dexamethasone will be reduced from 40 mg to 20 mg daily

Days 1, 4, 8 and 11 Bortezomib 1.3 mg/m^2 subcutaneous ***

Days 1, 8 Bendamustine 60 mg/m^2 intravenous infusion

Days 1-2, 4-5, 8-9 and 11-12 Dexamethasone 40 mg daily orally

The cycle is repeated every 3 weeks (21 days).

**For cycles 3-4 (and 5-6, where relevant) Bortezomib may be given as 1.3 mg/m^2 weekly for 3 weeks in a 21 day cycle in combination with Bendamustine and dexamethasone as per local practice. The dosing regimen used must be documented in the CRF.*

******or intravenous infusion****- see section 9.3 "route of Bortezomib administration"; if intravenous infusion is required due to participant intolerance of subcutaneous treatment, please contact the Chief Investigator and Trial Coordinator providing details for reasons for change.*

Arm B

Thalidomide, Bendamustine and Dexamethasone (BTD)

Participants > 70 years of age, the dose of dexamethasone will be reduced from 40 mg to 20 mg daily

Days 1 to 21 Thalidomide 100 mg daily p.o. preferably at night

Days 1, 8 Bendamustine 60 mg/m^2 intravenous infusion

Days 1-2, 4-5, 8-9 and 11-12 Dexamethasone 40 mg daily orally

The cycle is repeated every 3 weeks (21 days).

Total number of cycles (Arm A and B): All participants will receive four 21 day cycles. Autologous stem cell transplant (ASCT) as consolidation therapy is standard of care for <65 year old newly diagnosed patients. Participants not considered for ASCT, will continue on therapy in the form of BTD or BBD (based on their initial randomisation) up to a total of 6 cycles or significant toxicity.

9.1.1 Supportive Therapies

The following concomitant medications are permitted:

- **Co-trimoxazole 480 mg** - three times per week PO or alternative for PCP prophylaxis as per local institutional practice
- **Omeprazole 20 mg** - once daily PO whilst on dexamethasone
- **Metoclopramide 10-20 mg-** three times per day PO as required and on days of Bendamustine
- **Allopurinol 100 mg** - orally daily
- **Aciclovir 200 mg-** twice per day, orally

Thromboprophylaxis must be initiated for all participants on the BTD treatment arm and may be required for participants on the BBD arm based on risk assessment – consider use of Aspirin or Warfarin orally as LMWH is contraindicated at GFR <30 mls /min. However, if renal recovery occurs, participants can be switched to LMWH subcutaneously based on local practice.

The role of **anti-bacterial prophylaxis** is uncertain in these patients. Local protocols for antibiotic use should be adopted.

9.2 Dose Modifications

All dose reductions must be recorded in the relevant CRF.

9.2.1 Thalidomide Dose Modification:

Neuropathy: Thalidomide should be stopped or reduced if there are symptoms of progressive neuropathy causing functional disability. If the drug is stopped, re-introducing thalidomide after a 2 week gap at 50 mg/day with subsequent cautious dose escalation may be considered if symptoms permit.

9.2.2 Bortezomib Dose Modification:

Dose modifications for bortezomib will be based on the drug summary of product characteristics (SmPC). Dose reductions to 1.0 mg/m^2 and 0.7 mg/m^2 are permitted. If further reductions are required the bortezomib treatment should be stopped and further treatment options discussed with the Chief Investigator.

Dose reduction for neuropathy grade 2 with pain or grade 3 attributed to bortezomib should be reported as an SAE as detailed in Section 10.6.

9.2.3 Bendamustine Dose Modification:

Myelosuppression: If the neutrophil count falls below 1.0 x 10^9/L with therapy, or platelets below 50 x 10^9/L, bendamustine should be temporarily discontinued. Start participants on G-CSF and platelet support until counts recover (Neutrophils > 1.0 x10^9/l and platelets >50 x 10^9/l); consider reintroducing bendamustine at 50% of original dose. If dose reduction is employed please record this on the relevant CRF.

Renal Impairment: a 50% dose reduction should be implemented for patient participants with a GFR of less than 10ml/min

9.2.4 Dexamethasone Dose Modification:

A dose reduction in dexamethasone should occur only for Grade 3 or 4 corticosteroid toxicities.
Dexamethasone should be reduced to 20 mg per day if dose reduction is required. Further dose levels of 10 mg daily and 5 mg daily can also be considered if there is on-going toxicity. In exceptional circumstances, subjects may not tolerate sudden steroid withdrawal at the end of 4 days of dexamethasone therapy. In such an instance, and after the first cycle, a tapering regimen of dexamethasone (10 mg on day 5; 6 mg on day 6; 2 mg on day 7 then stop) can be prescribed.

9.3 Bortezomib Route of Administration

A small proportion of participants on subcutaneous bortezomib experience local site reactions. If a Principal Investigator (PI) wishes to switch a participant from subcutaneous to intravenous injection, due to intolerance, it must be recorded as an Adverse Event in the CRF. The PI should change the injection site at the next infusion and if the participant remains intolerant, record as an Adverse Event and contact the Chief Investigator (CI), via the Trial Coordinator, with all relevant information. The CI will review the information provided. If the Chief Investigator approves the switch, the Trial Coordinator will forward the recommendation to Janssen–Cilag Ltd for their approval. If approved, Janssen-Cilag will provide participant specific stock of the drug to the site pharmacy via B&C. If a route change is employed it must be recorded in the relevant CRF. jSee Appendix J for a flow chart summarising switch of route of administration.

9.4 Irradiated Blood Products

Bendamustine is a bifunctional agent with antimetabolite and alkylating agent properties. It is mandatory that all participants treated in this trial receive irradiated blood products to prevent transfusion associated graft versus host disease.

9.5 Labeling, Storage, Accountability and Ordering of Study Drugs

9.5.1 Ordering of Study Drugs

9.5.1.1 Bortezomib

Upon site activation, the OPTIMAL Trial Office will inform B&C and confirm site set up for supply of bortezomib. The site pharmacist will need to order the initial supply of Bortezomib for subcutaneous administration. Site pharmacies should ensure they have sufficient stock of Bortezomib SC stored at site ready to be allocated at participant registration and randomisation. We recommend ordering sufficient drugs for the first cycle of treatment; one carton of Bortezomib SC (10 blistered vials, 3.5 mg each).

Each site pharmacist will request supply of bortezomib by faxing or emailing the completed OPTIMAL Trial drug order form to the OPTIMAL Coordinating Team on the details below. The Trial Coordinator will review and approve the shipment to be released from B&C. Confirmation of shipment from B&C will be sent by email to site pharmacists and the Trial Coordinator. Please allow a minimum of 7 working days from order date for delivery.

Drug Ordering (Bortezomib)

Please send completed OPTIMAL drug order form to OPTIMAL Trial Team:

Email:**OPTIMAL.trial@nhs.net**

Please allow a minimum of 7 working days from order date for delivery

OPTIMAL Trial Office will request a monthly log of trial drug distribution from B&C for monitoring purposes.

9.5.1.2 Bendamustine, Thalidomide, Dexamethasone

Sites should obtain bendamustine, thalidomide and dexamethasone directly from local pharmacy stock in accordance with local procedures and guidelines. It is the responsibility of site pharmacies to ensure sufficient stock of bendamustine, thalidomide, dexamethasone is stored locally for participants on trial.

9.5.2 Labeling of Study Drugs

Bortezomib and thalidomide are registered as Investigational Medicinal Products (IMPs) in this trial. B&C Group will distribute bortezomib centrally directly to trial sites with trial specific labels in accordance with current regulatory requirements.

Thalidomide will be sourced locally at individual trial sites as per routine practice. Site pharmacists will be responsible for labeling thalidomide for trial use in accordance with regulation 46 SI2004/1031 and detailed

guidance provided in Annex 13 of the EU Good Manufacturing Practice Guide. Sites will be provided with a label for use as part of the trial.

Bendamustine and dexamethasone are registered as non-Investigational Medicinal Products (nIMPs) in this trial. Both bendamustine and dexamethasone will be sourced locally at individual trial sites as per routine practice and do not require labelling for trial use.

9.5.3 Storage and Dispensing of Study Drugs

Please refer to the current SmPCs for details of storage for unopened and reconstituted products. Sites should follow their own local SOPs for storage and temperature monitoring. Storage records for all trial drugs must be maintained and made available for review on request. Any temperature excursions whilst stored on site must be reported to the Sponsor (via the Trial Coordinator). Affected stock should be quarantined and must not be used until the affected stock is verified as suitable for use. The decision on suitability of IMP will be made by the drug provider and confirmed by the Trial Office to sites, ensuring the Sponsor is made aware. For further details on this please see the OPTIMAL Pharmacy Manual.

The study drugs will be dispensed as per standard Clinical Trials procedures from the hospital pharmacy. It is not feasible to blind the randomisation as one treatment contains an intravenous component.

9.5.4 Accountability of Study Drugs

It is the responsibility of the local pharmacists to ensure full drug accountability records are maintained for all IMPs (bortezomib and thalidomide). For further details of requirements please refer to the Pharmacy Manual. Records of accountability may be requested by Sponsor or OPTIMAL Trial Coordinating Team for monitoring purposes. No pharmacy accountability of bendamustine and dexamethasone will be required for this trial, although participants will be required to complete Participant Treatment Diary Card(s) for dexamethasone and thalidomide assessing participant compliance (see Section 9.6).

9.5.5 Unavailability of Study drug

If due to unforeseen or exceptional circumstance a trial specific drug is not available, commercial stock can be used on the condition that it is confirmed that the trial specific and commercial stock are identical in terms of manufacturing and product quality. Sites must contact Sponsor and OPTIMAL Coordinating Team who will review the circumstances and use of commercial stock. This would need to be approved by CI and Sponsor prior to implementation. Both CI and Sponsor must be notified when trial stock is available for use again. The cost of this will be the responsibility of the individual host organisation.

9.6. Participant Compliance and Treatment Diary Card(s)

Bendamustine and bortezomib will be administered on site. Any reasons for non-administration should be documented in the relevant CRF. Thalidomide and dexamethasone are dispensed to participants. Participants will be requested to return all empty, unused or part used thalidomide and/or dexamethasone medication and packaging from used medication at each visit to the researcher. The researcher will record any unused medication in the relevant CRF, prior to returning the drugs to pharmacy.

Participants will also be given a Participant Treatment Diary Card by the researcher to complete for each cycle of thalidomide and/or dexamethasone. This must be completed by the participant to confirm that all doses were taken and if any were missed to record the details and reason.

Participants randomized to Arm A (bortezomib, bendamustine and dexamethasone) will only complete a Treatment Diary Card for dexamethasone. Participants randomized to Arm B (thalidomide, bendamustine and dexamethasone) will need to complete Treatment Diary Cards for both dexamethasone and thalidomide.

The Treatment Diary Card(s) should be collected at the end of each cycle of treatment and returned to the OPTIMAL Trial Office with the accompanying Treatment CRF. Site staff should also retain a copy locally.

9.7 Study Drug Destruction

Destruction of any returned participant medication should be completed as per local procedures once accountability and compliance checks have been completed. Confirmation of destruction may be requested by OPTIMAL Trial Team for monitoring purposes.

9.8 Concomitant Medication

Details of any concomitant medication (any medication, other than the trial product, that is taken during the trial) should be recorded at trial entry (i.e. Screening) and then again on the first and last day of each treatment cycles.

Any changes in concomitant medication during treatment cycles should be recorded at the end of week 3 of each treatment cycle. Any changes in concomitant medication between trial visits (i.e. between Screening and first treatment cycle, or between two different treatment cycles) should be recorded on day of the next treatment cycle.

If there has been no change in concomitant medication please state this clearly on relevant CRF.

If any change influences the participant's eligibility to continue in the trial, as per inclusion/exclusion criteria, the Chief Investigator and/or Trial Coordinator must be informed and any withdrawal documented on the relevant Withdrawal CRF (see section 7.8).

9.9 Post-trial Treatment

Participants will be deemed to have completed the trial when they have completed the 12 month follow-up post randomisation. Participants should discuss further treatment and continuing care with their clinician and clinical care team.

Please refer to the "**Pharmacy Manual**" for further details on IMP and pharmacy related procedures and requirements.

10. SAFETY REPORTING

10.1 Definitions

Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences not necessarily caused by or related to that product.
Adverse Reaction (AR)	An untoward and unintended response in a participant to whom an investigational medicinal product has been administered, which is related to any dose administered to that participant. The phrase "response to an investigational medicinal product" means that a causal relationship between a trial medication and an AE is at least a reasonable possibility, i.e. the relationship cannot be ruled out. All cases judged by either the reporting medically qualified professional or the Sponsor as having a reasonable suspected causal relationship to the trial medication qualify as adverse reactions.
Serious Adverse Event (SAE)	A serious adverse event is any untoward medical occurrence that: • results in death • is life-threatening* • requires inpatient hospitalisation or prolongation of existing hospitalisation** • results in persistent or significant disability or incapacity • consists of a congenital anomaly or birth defect. • Other medically important event e.g. pregnancy (see section 9.6)*** *The term "life-threatening" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. ** “Hospitalisation” is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition (including elective procedures that have not worsened) do not constitute an SAE. *** “Other medically important events” may not be immediately life threatening or result in death or hospitalisation, but may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences (e.g. suspected transmission of an infectious agent by a medicinal product is a serious event). Medical judgment should be exercised in deciding whether an AE/AR or other important medical event require expedited reporting. Any AE is considered serious if it is associated with clinical signs and symptoms judged by the investigator to have a significant clinical impact
Serious Adverse Reaction (SAR)	An adverse event that is both serious and, in the opinion of the reporting Investigator, believed with reasonable probability to be due to one of the trial treatments, based on the information provided.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medicinal product in question set out: • in the case of a product with a marketing authorisation, in the summary of product characteristics (SmPC) for that product (OPTIMAL Study) • in the case of any other investigational medicinal product, in the investigator’s brochure (IB) relating to the trial in question.

NB: To avoid confusion or misunderstanding of the difference between the terms "serious" and "severe", the following note of clarification is provided: "Severe" is often used to describe intensity of a specific event, which may be of relatively minor medical significance. "Seriousness" is the regulatory definition supplied above.

Any pregnancy occurring during the clinical trial and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect, at which point it would fall within the definition of "serious". Please refer to Section 10.9 for procedures in the case of pregnancy.

10.2 Assessment of Causality

The relationship of each adverse event to the trial medication must be determined by a medically qualified individual according to the following definitions:

Classification	Definition
Drug Related (Related)	The adverse event follows a reasonable temporal sequence from trial medication administration. It cannot reasonably be attributed to any other cause.
Not Drug Related (Unrelated)	The adverse event is probably produced by the participant's clinical state or by other modes of therapy administered to the participant.

10.3 Assessment of Expectedness

Expectedness will be determined using the current Summary of Product Characteristics (SmPC) for each drug. SmPC's are also available using the following link: http://www.medicines.org.uk/emc/

It is the responsibility of the site staff to make sure the most recent version of the SmPC is used when assessing expectedness. Updated SmPC's will be provided to sites by the Trial Office.

If there are any updated SmPC's for any of the trial drugs, the CI will review and assess whether there are any clinically significant changes. If there is a significant change on review by the CI, these will be submitted as a substantial amendment to regulatory authorities. If there is no significant change, these updated SmPC's will be submitted with the next DSUR.

10.4 Terminology and Assessment of Severity

An adverse event term must be provided for each serious adverse event or adverse reaction, preferably using the Short Name as listed in the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). Severity of each Adverse Event or Reaction must be determined by using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE) as a guideline, wherever possible. The criteria are available online at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

In those cases where the CTCAE criteria do not apply, severity should be coded according to the following criteria: 1 = Mild 2 = Moderate 3 = Severe and recorded on CRF

10.5 Reporting Non-Serious Adverse Events

All non-serious Adverse Events, whether expected or not, occurring during the time period from randomisation until the final study visit (12 months post-randomisation) that are observed by the Investigator, or reported by the participant, must be recorded on the relevant CRF, whether or not attributed to trial medication. The following information should be recorded: description of event, date of onset and end date, severity, assessment of relatedness to trial medication and outcome. Follow-up information should be provided as necessary as soon as available.

The severity of events will be assessed using the Common Terminology Criteria for Adverse Events V 4.03 (CTCAE) as a guideline, wherever possible and using the following scale: 1 = mild, 2 = moderate, 3 = severe.

The CTCAE criteria are available online at:
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

AEs considered related to the trial medication as judged by a medically qualified investigator or the Sponsor must be followed up either until resolution, or until the event is considered stable.

It will be left to the Investigator's clinical judgment to decide whether or not an AE is of sufficient severity to require the participant's removal from treatment. A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these situations occurs, the participant should undergo an end of trial assessment and be given appropriate care under medical supervision until symptoms cease, or the condition becomes stable. The researcher should record details on the Withdrawal CRF and continue to follow-up the participant as per the trial protocol, unless specifically requested otherwise by the clinician or participant.

10.6 Reporting Serious Adverse Events

All SAEs must be reported immediately (within 24 hours of awareness) during the time period from randomisation to 30 days following last administration of IMP. Please note: this period is 24 working hours so if a site becomes aware of an SAE on Friday it can be reported on the Monday, although it is advised to send as soon as possible.

Each SAE must be reported on OPTIMAL SAE Reporting Form. When reporting an initial SAE the 'initial' box must be checked to indicate an initial report and the following minimum information is required: description of event, date of onset, severity, and assessment of causality and relatedness to trial medication. A separate SAE Form should be used for each SAE.

The SAE Form must be signed by the site Investigator (consultant name on the Site Signature and Delegation Log who is responsible for the participant's care). The Investigator must assess the severity, causality and expectedness of the event. In the absence of the responsible investigator the form should be completed and signed by another suitably qualified member of the site trial team. The responsible investigator should subsequently check the SAE form, make changes as appropriate, sign and then send to the OPTIMAL Trial Coordinator as soon as possible by secured email using the details below:

SAE REPORTING

Please send all SAE Forms to OPTIMAL Trial Team within 24 hours of becoming aware of event:

Email:**OPTIMAL.trial@nhs.net**

(Mon-Fri, 9am to 5pm, excluding public holidays or dates when notice has been given by the Trial Coordinator)

The OPTIMAL Trial Coordinator will confirm receipt of the SAE Reporting Form and provide a unique SAE Reference Number as confirmed by the Sponsor. This SAE reference number should be added to all SAE documentation and be quoted in all follow-up correspondence.

Follow-up information should be reported on a blank OPTIMAL SAE Reporting Form by ticking the box marked 'follow-up', including follow up information and an end date and outcome when known. Participants must be followed-up until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilised.

Sites should refer to Safety Reporting guidance document provided by OPTIMAL Trial Office and contact CI or Trial Coordinator to discuss any queries or issues relating to AE's or SAE's.

10.7 Foreseeable Events that DO NOT require reporting as an SAE

The following table lists foreseeable events that fulfill the definition of an SAE related to myeloma and its treatment and but **do not** require expedited reporting as an SAE for this trial.

Foreseeable SAE's which **do not** require expedited reporting as an SAE for this trial must be recorded in the relevant section(s) of the CRF.

Table 10.1. Forseeable Events that fulfill the definition of an SAE but do not require expedited reporting for this trial.

Foreseeable Events that DO NOT require expedited reporting as an SAE for this trial These SAE's should be recorded on relevant CRF.
Disease progression
Disease related deaths
Routine treatment or monitoring of the studied indication not associated with any deterioration in myeloma condition
Treatment, which was elective or pre-planned, for a pre-existing condition, not associated with any deterioration in myeloma condition
Hospitalisation for palliative care
Grade 1-4 haematological toxicity is an expected consequence of effective treatment, and is only required to be reported if it fulfills the criteria of an SAE as defined above (see Section 9.1)
Treatment (including hospitalisation, or extension of hospitalisation) for transfusions or pain relief
Surgical interventions for skeletal related events, e.g. fixation of fractures, vertebroplasty
Increased bone pain
Febrile neutropaenia
Alopecia

10.8. Foreseeable SAEs that DO require immediate reporting as SAEs

The following table lists foreseeable events that fulfill the definition of an SAE related to myeloma and its treatment which **do** require expedited reporting as an SAE for this trial.

Foreseeable SAE's which **do** require expedited reporting as an SAE for this trial must be reported on an SAE Reporting Form as per protocol (see section 10.6). These should be reviewed and assessed for severity, relatedness and causality by a medically qualified person.

Table 10.2. Forseeable Events that fulfill the definition of an SAE that do require expedited reporting for this trial.

Foreseeable Events that DO require expedited reporting as an SAE for this trial These SAE's should be reporting immediately using an SAE Reporting Form
Hyperglycaemia grade 3 or above
Neuropathy grade 2 with pain or grade 3
Venous thromboembolism
New bone fractures or spinal cord compression during therapy
Development of any grade 4 non-haematological toxicity (excluding alopecia)

Sites should refer to the current Summary of Product Characteristics (SmPC) for each drug for more specific details and potential drug interactions. Please see the OPTIMAL Pharmacy Manual for further details.

10.9 Procedures in Case of Pregnancy

If a female participant or the partner of a male participant becomes pregnant at any time from the date of randomisation to 30 days after final study drug administration, the pregnancy must be reported to the OPTIMAL Trial Coordinator within the same timelines as an SAE and classified as an "other medically important event" on the SAE Reporting Form. Both a completed SAE Reporting Form and Pregnancy Report Form A CRF (Appendix H) must be submitted to the Trial Coordinator by secured email within 24 hours of awareness. The Investigator should seek consent to report information regarding the outcome of the pregnancy from the mother.

10.9.1 Pregnancy Follow-Up Reports

All pregnancies should be followed-up until an outcome is determined (if participant consent is given). Follow-up Pregnancy Report Form B CRF (Appendix I) must be submitted to the OPTIMAL Trial coordinator by secured email within 1 business day of learning of the outcome. Reports must include an evaluation of the possible relationship of the trial treatment to the pregnancy outcome.

10.9.2 SAEs During Pregnancy

Any SAE occurring during pregnancy must be reported using the SAE Reporting Form, according to SAE reporting procedures detailed in Section 10.6.

10.9.3 Pregnancy Report Processing at Sponsor site

The OPTIMAL Trial Coordinator will submit all Pregnancy Reports concerning participants or partners who have received or have been exposed to any IMPs to Janssen-Cilag (Bortezomib only) and the Sponsor Representative (Oxford University Hospitals NHS Foundation Trust R&D department) within 24 hours of awareness. The CI with the Sponsor will submit a report to the MHRA and REC should the pregnancy outcome meet the definition of a SUSAR.

10.10 SUSAR Reporting

All SUSARs will be reported by the CI to the relevant Competent Authority, REC and any other parties as applicable. For fatal and life-threatening SUSARS, this will be done no later than 7 calendar days after the Sponsor or delegate is first aware of the reaction. Any additional relevant information will be reported within 8 calendar days of the initial report. All other SUSARs will be reported within 15 calendar days.

Principal Investigators will be informed of all SUSARs for the relevant IMP for all studies with the same Sponsor, whether or not the event occurred in the current study.

10.11 Review of SAEs

10.11.1 OPTIMAL Trial Office and Sponsor Responsibilities

The joint Oxford University Hospitals NHS Foundation Trust / University of Oxford Trials Safety Group (TSG) will conduct a review of all SAEs for the trial reported during the quarter and cumulatively. The aims of this committee include:

- To identify any trends, such as increases in un/expected events, and take appropriate action
- To seek additional advice or information from investigators where required
- To evaluate the risk of the trial continuing and take appropriate action where necessary

The Trial Coordinator will forward all SAEs to the Chief Investigator and the Sponsor representative (Oxford University Hospitals NHS Foundation Trust R&D department) who will perform an initial check of the report, request any additional information, and ensure it is reviewed by the Sponsor's medically qualified Medical Monitor, with oversight and input from the Chief Investigator. All SAEs will also be reviewed at the Trial Safety Group meeting.

Additional and further information, including follow-up or corrections to the original case, will be requested from site staff by the Trial Coordinator as required and forwarded to the Chief Investigator and Sponsor Representative.

Oxford University Hospitals NHS Foundation Trust is undertaking the duties of trial Sponsor and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA) and the research ethics committees as appropriate.

The OPTIMAL Trial Office and Sponsor will keep all investigators informed of any safety issues that arise during the course of the trial.

10.11.2 Development Safety Update Reports (DSURs)

The CI will submit (in addition to the expedited reporting detailed above for SAE's and SUSAR's) Development Safety Update Report (DSUR's) once a year throughout the clinical trial, or on request, to the Competent Authority (MHRA in the UK), Research Ethics Committee (REC), host NHS Trust and Sponsor. A copy will be sent to sites for filing locally in site files.

10.11.3 Safety Reporting Responsibilities to Janssen-Cilag

The Sponsor, Chief Investigator, or suitably delegated individuals, will submit to the identified representative of Janssen the following safety information for participants receiving bortezomib (Arm A):

- Copies of all SAEs reported during the study for participants randomized to receive bortezomib (Arm A)
- Details of all AE's reported during the study for participants randomized to receive bortezomib (Arm A), provided annually and in a final report within 6 months of completion of treatment of last participant
- Copies of annual trial specific Development Safety Update Reports (DSURs) sent to the Competent Authorities and Research Ethics Committees (following causality and expectedness assessments made as applicable for the current study sponsored by the institution and/or principal investigator);
- The Sponsor and Chief Investigator shall notify Janssen-Cilag immediately in case of a suspension of recruitment or premature cessation of the concerned clinical study because of a safety concern; preferably by means of a telephone contact with the Company Representative, alternatively by fax within 24 hours of the decision;

11. DATA AND SAFETY MONITORING COMMITTEE (DSMC)

A Data and Safety Monitoring Committee (DSMC) will remain in place throughout the study and hold a meeting at least once annually.

11.1 Primary Responsibilities of the DSMC

To safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, and monitor the overall conduct of the clinical trial.

The DSMC remit will include making recommendations to the Trial Steering Committee (TSC) (see section 12). The DSMC will receive and review the progress and accruing data of this trial and provide advice on the conduct of the trial to the TSC. The DSMC should inform the Chair of the TSC if, in their view:

- there are concerns about the safety of one or more of the treatment arms
- the results show a benefit of one treatment arm over another that is so large, and precise, that it is likely to convince a broad range of clinicians to change practice
- it is evident that if the trial continued it would fail to show a clear benefit for any treatment arm
- accrual is so low that it is unlikely that a sufficient number of participants would be recruited to provide meaningful results

Interim analysis will take place after 60 participants (who have completed at least 2 cycles of treatment) have been recruited. During interim analysis, the DSMC will review the data unblinded to the treatment arms and may make recommendations to amend or terminate the trial if there are unacceptable toxicities or excess of events in one treatment arm. In addition, participant safety will be reviewed assessing the reported toxicity for the recruited cohort of participants.

11.2 Membership of the DSMC

The DSMC is an independent group consisting of clinicians and other appropriate professionals who have pertinent experience in the management of adult participants with haematological cancer, particularly participants diagnosed with multiple myeloma, as well as in the conduct and monitoring of randomised clinical trials. A DMC Charter outlines the roles and responsibilities of the DMC. Each member of the DSMC is expected to serve until a final assessment of safety data is completed.

12. TRIAL STEERING COMMITTEE (TSC)

A TSC comprising of an independent chair, the Chief Investigator, Trial Coordinator, representative of the Sponsor and at least one other clinician not directly associated with the trial, will remain in place throughout the study.

The TSC will provide advice and oversight on trial management and any trial related issues. The roles and responsibilities of the TSC are outlined in the TSC charter.

The TSC will consider the advice of the DSMC and may consider discontinuing the trial if the recruitment rate or data quality are unacceptable or if the trial compromises participant safety in any way. The TSC may also recommend that the trial stop early if the interim analyses (60 participants who have completed at least 2 cycles) showed differences between treatments in terms of efficacy.

The TSC will meet at least once annually although may meet more frequently to discuss specific issues arising, or in e event of any concerns.

13. STATISTICS

Data presented in December 2011 at the American Society of Haematology conference from a single centre retrospective analysis of 112 patients presenting with renal impairment in Greece suggests that bortezomib (n=30 patients) containing regimens act more rapidly than thalidomide containing regimes (n=53 patients) with significant differences in response (83% vs 61%) (34). In addition, a retrospective analysis of 54 patients not uniformly treated from 18 centres in 10 countries showed that 73% of patients demonstrated a reduction in sFLC over the course of treatment with 86.7% of these patients (i.e. 63% of all patients) demonstrating decreased sFLC levels by day 12 (35). Bortezomib patients had a median reduction of 79% by day 12 compared to 66% in the thalidomide patients. This was a retrospective audit and some patients may have received a combination of thalidomide and bortezomib. There were centres which also employed different types of high cut off dialysers and it is not yet clear if that plays an important role in reduction of sFLC.

These data imply that a 35% difference between treatment arms may not be achieved. Recruiting 60 patients in each arm can detect a more realistic lesser difference between treatment arms. This will allow

the detection of 23% differences in the percentage of patients achieving >50% reduction in sFLC between treatment arms, e.g. from 60% to 83%, with 80% power and a 5% 2-sided significance level, assuming no drop-out. This will also allow the detection of 24% differences in the percentage of patients achieving >50% reduction in sFLC between treatment arms e.g. from 60% to 84%, with 80% power and a 5% 2-sided significance level, assuming 10% drop-outs.

For the secondary endpoint of percentage reduction in sFLC, 55 patients on each arm would allow the detection of a standardised difference of 0.55 or greater with 80% power and a 5% 2-sided significance level. This is just looking at the results at one time point and we will also undertake longitudinal analysis for each patient to explore changes over time. These data will be logged in order to accommodate the expected extreme values.

13.1 Interim Analysis

There are no formal stopping rules for the trial since 120 participants are needed to be able to detect the 23% expected difference between treatments. However an interim analysis is planned once the first 60 participants have been randomised into the trial and completed at least 2 cycles of chemotherapy. The interim analysis will assess the proportion of participants achieving >50% reduction in sFLC following two cycles of chemotherapy in order to test the power calculation assumptions.

In addition, participant safety will be reviewed assessing the reported toxicity for this first cohort of 60 participants. The DSMC will review the data unblinded to the treatment arms and may make recommendations to amend or terminate the trial if there are unacceptable toxicities or excess of events in one treatment arm.

13.2 Final Analyses

The proportion of participants achieving varying levels of sFLC response at the end of 2 cycles of treatment will be compared using a chi-squared test. The secondary endpoints of sFLC response, renal response, toxicity and survival will be assessed once all participants have been followed up for at least 12 weeks (or until withdrawn).

Survival will be calculated from the date of consent to the date of death within the first 12 weeks (or up to week 18 for those participants receiving cycles 5 & 6) , or censored as alive at 12 weeks if death occurred after this time or if no date of death was recorded. Kaplan-Meier curves will be compared across treatments and median survival will be estimated for each treatment group both unadjusted and adjusted for age and CKD 4/5.
Prediction model for renal recovery based on sFLC response will be explored using multivariate techniques with adjustment for treatment, age, CKD 4/5 and other clinical factors as appropriate.

13.3 Patient Reported Outcomes

Patient Reported Outcomes will be measured using validated EuroQoL Quality of Life (EQ-5D-3L) Heath questionnaires (38). Participants will be asked to complete a questionnaire on day 1 of each treatment cycle and at 1 month and 12 month follow up visits. Summary statistics will be used to assess change from baseline to follow up.

13.4 Termination of the Trial

In the event that the trial is terminated early; all participants will be advised accordingly and local investigators should discuss with participants a return to standard NHS care.

The trial will be terminated prematurely if:

- Mandated by the Research Ethics Committee
- Mandated by the Competent Authority (MHRA in UK)
- Following recommendations from the Data and Safety Monitoring Committee (DSMC)
- The interim analysis does not support the continuation of the study
- There are safety issues which cannot be resolved
- The study is unlikely to capture creditable data
- Funding for the trial ceases
- Withdrawal of Sponsorship or NHS permission

The Sponsor, regulatory authorities, and site investigators will be advised and the requisite forms completed and submitted according to regulatory timelines.

If the trial has been concluded or terminated early, the CI in conjunction with the Sponsor, must ensure the Research Ethics Committee and Competent Authority (MHRA in the UK) is notified in writing within 15 days of the decision. Funders or any other relevant parties will also be notified in writing.

13.5 Inclusion in Analysis

Participants who fulfil the eligibility criteria, consent to take part in the study, are randomised, and receive at least two cycles of treatment will have their data included in the study analysis. In the event that a participant has withdrawn from the trial, any existing data can be used in data analysis.

14. DATA MANAGEMENT

14.1 Source Data

Source documents are where data is first recorded, and from which participants' CRF data is obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

14.2 Case Report Forms (CRF's) and Data Recording

All trial data will be entered onto paper CRFs at sites and transferred to OPTIMAL Coordinating Centre where it will be entered into a validated database. Sites will not have access to the trial database and all data will be entered centrally at Oxford. Hardcopy copies of CRF's will be filed securely at OPTIMAL Trial Coordinating Centre and electronic copies will also be taken. Every effort should be made to complete trial documentation as fully as possible and in accordance with the protocol. OPTIMAL Trial Coordinating team will contact sites to request any missing or additional information and this should be provided in a timely manner.

At randomisation participants will be assigned a unique Study ID No. which will be used alongside Participant Initials and Date of Birth to identify the participant on all trial documentation. Identifiable data will not be included in any trial documentation or the database. Sites should ensure that participant Study ID No. is clearly written on each page of each CRF and that separate CRF's are secured so that it is clear which CRF relates to which participant. Sites should ensure copies of all CRF's are taken **before** posting and filed locally to avoid any loss of data.

Sites should send completed CRF's via secure post to the OPTIMAL Coordinating Centre using the contact details below. Screening, Eligibility and Randomisation CRF's should be sent immediately to OPTIMAL Coordinating Centre via secure email, with hardcopies to follow via post. Randomisation Forms should also be sent to Warwick CTU via fax, if not using telephone randomisation (see section 7.4). Treatment CRF's, including QoL questionnaire and Participant Treatment Diary Cards can be sent in batches via post to OPTIMAL Coordinating Centre, preferably at the end of each treatment cycle. 1 month Follow UP CRF's, including QoL questionnaire and Participant Treatment Diary Cards, and 12 month Follow UP CRF should be sent via post to the Coordinating Centre upon completion of CRF.

The relevant Central Laboratory Sampling CRF should be sent with the participant samples, and a copy also sent to OPTIMAL Coordinating Centre via post in batches. A copy of the participant Informed Consent Form must also be sent for both Oxford and Birmingham Central samples (see section 8)

Adverse Events CRF's can be sent in batches alongside associated CRF's. Serious Adverse Event CRF's must be sent immediately as per SAE Reporting procedures (see section 10.6).

In the case of Participant Transfer, Death or Withdrawal (see section 7.8), sites should complete and send the relevant completed CRF via post to the Coordinating Centre as soon as they become aware of the change. If the Death may be related to an SAE sites should gather required information as soon as possible to complete the SAE and Death Form. Withdrawal Forms should be completed as soon as possible after a withdrawal decision has been made.

Copies of Informed Consent Forms should be sent only via secure email address, or if sent via post should be sent separately to any study documentation to ensure anonymity. Original signed Consent Forms should be retained at sites.

If frequent postage is an issue for sites, sites can email copies of CRF's and send original copies in periodical batches. This is excluding screening, eligibility and randomisation forms which must be sent prior to a participant entering the trial.

Sending CRF's and Documents

OPTIMAL Coordinating Team
Late Phase Haematology Research Team
Churchill Hospital
Headington
Oxford, OX3 7LE

Email: OPTIMAL.trial@nhs.net

14.3 Archiving

All trial documentation should be archived at site as per local NHS guidelines before being destroyed. OPTIMAL Trial Team will contact sites to arrange for the transfer of any relevant documentation relating to study close-down and archiving.

15. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, ICH GCP, and all other relevant regulations and standard operating procedures.

15.1 Monitoring and Audit

Sponsor representative monitors from Oxford University Hospitals NHS Foundation Trust and regulatory authority inspectors are responsible for contacting the Chief Investigator for the purpose of monitoring.

The monitor is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol and GCP; completeness, accuracy, and consistency of the data and, on the conduct of clinical research. The monitor should have access to participant medical records and other study-related records needed to verify the entries on the CRFs. The monitor will ensure that all data is handles according to the Data Protection Act (1998) and that participant confidentiality is respected.

The investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved. Any discrepancies found between source documents and completed CRFs will be addressed by the study site. Every effort should be made to account for any missing data from the CRF.

OPTIMAL Coordinating Trial team will contact sites at least once annually for the purposes of monitoring, either remotely or in person. There may also be additional triggered monitored visits if there is cause for concern or a specific issue has been identified. In all cases sufficient notice will always be given and a time convenient for all parties agreed. OPTIMAL Trial Coordinating Team will monitor only anonymised trial documentation and will not access or verify identifiable information or medical notes.

16. SERIOUS BREACHES

The Medicines for Human Use (Clinical Trials) Regulations (Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928) contains a requirement for the notification of "serious breaches" to the MHRA within 7 days of the Sponsor becoming aware of the breach.

A serious breach is defined as “A breach of GCP or the trial protocol which is likely to effect to a significant degree –

(a) the safety or physical or mental integrity of the subjects of the trial; or

(b) the scientific value of the trial”.

In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the REC committee, Regulatory authority and NHS host organisation within 7 calendar days.

17. ETHICAL AND REGULATORY CONSIDERATIONS

17.1 Declaration of Helsinki

The Investigator will ensure that this trial is conducted in accordance with the principles of the Declaration of Helsinki.

17.2 ICH Guidelines for Good Clinical Practice

The Investigator will ensure that this trial is conducted in full conformity with relevant regulations and with the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996.

17.3 Approvals

The Investigator, in association with the Sponsor, will ensure all relevant regulatory approvals are met and maintained throughout the study, including approvals from Research Ethics Committee (REC), Competent Authority (MHRA in UK) and local NHS permissions.

17.4 Reporting

The Chief Investigator shall submit once a year throughout the clinical trial, or on request, an Annual Progress Report to the REC, host organisation and Sponsor. In addition, an End of Trial notification and final report will be submitted to the MHRA, the REC, host organisation and Sponsor. Copies of submitted reports will be disseminated to sites for local sites.

OPTIMAL Trial Coordinating Centre will also submit reports to funders and any other individuals and groups as required or as outlines in any contractual agreements.

17.5 Access to Data and Confidentiality

All participant data will be regarded as strictly confidential and will be handled and stored securely in accordance with ICH-GCP and relevant regulations and legislations, including Data Protection Act (1998).

Local Investigators are responsible for ensuring trial documentation and participant data at each of their own sites is handled according to all relevant regulatory and legislative guidelines. Any individual or party related to the trial and accessing trial data will be bound by confidentiality agreements. Warwick Clinical Trials Unit will maintain confidentiality of all participant data and will not disclose information by which participants may be identified to any third party, other than those directly involved with the treatment of the participant. Funders and pharmaceutical companies will not have access to any identifiable participant data.

On all trial-specific documents, other than the signed consent form, the participant will be referred to using only Study ID No. and participant initials and date of birth; not by name. Any documentation detailing identifiable data such as signed Informed Consent Forms must be filed separately from any trial data such as CRF's and transferred using only secure methods (see section 14.2)

All clinical information will be securely stored and will only be accessible by authorized personnel for the purposes of this study. Direct access to personal data will be granted to authorised representatives from the Sponsor, host institution and the regulatory authorities to permit trial-related monitoring, audits and inspections. This will be detailed on the PIS and Informed Consent Form.

Participants will be asked to consent fo their General Practitioner (G.P.) to be informed of their participation in the study and for information to be shared with medical staff if relevant to participant's clinical care.

Central Laboratory Samples sent to Birmingham will include participant identifiable data in order to produce a report for the PI which may influence participant treatment or care. This report will only be available to the clinical care team and if filed in trial documentation will be anonymised using particpant Study ID as per protcool (see Section 8.3). Samples sent to Oxford will be link-anonymised so that only the individual research sites will be able to identify participants from a log they will maintain which will identify individuals.

17.6 Expenses and Benefits

Participants will not receive any remuneration for participating in this trial.

18. FINANCE AND INSURANCE

18.1 Funding

OPTIMAL is an investigator-led study funded by Janssen- Cilag and Bloodwise ((formerly Leukaemia and lymphoma Research). The study has previously been supported by NAPP Pharmaceuticals.

18.2 Indemnity and Insurance

NHS bodies are legally liable for the negligent acts and omissions of their employees. If a participant is harmed whilst taking part in a clinical trial as a result of negligence on the part of a member of the trial team, this liability cover would apply.

Non-negligent harm is not covered by the NHS indemnity scheme. The Oxford University NHS Foundation Trust, therefore, cannot agree in advance to pay compensation in these circumstances. In exceptional circumstances an ex-gratia payment may be offered.

18.3 Publication Policy

The results of the trial will be reported in a peer reviewed journal on behalf of all collaborators and investigators. The trial collaborators will draft the main report, and the sponsor, before submission for publication, will agree the final version.

Authorship and accountability:

As per ICMJE guidelines an author is generally considered to be anyone who provides substantive intellectual contributions to a published study. Specifically, authorship credit should be based on:

1. substantial contributions to study conception and design, or acquisition of data, or analysis and interpretation of data, *and*
2. drafting the article or revising it critically for important intellectual content, *and*
3. final approval of the version to be published.

All three conditions should be met.

Conversely, individuals who do not contribute in this manner do not warrant named authorship. Individuals who do not meet criteria for authorship but who contributed materially to the manuscript will be recognized in acknowledgments when the manuscript is published. In some cases, journals recognise contributors rather than authors. Subject to journal policy, we will list the names of all investigators at the end of a manuscript. The lead author is generally responsible for defending the content and the integrity of the manuscript when submitted to a journal.

The success of the trial depends on the collaboration of all participants. Equal credit will be given to those who have wholeheartedly collaborated in the trial. The trial will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (www.consort-statement.org). A copy of the final report will be sent to the sponsor.

19. REFERENCES

1. [cited 2012 25/02]; Available from: http://info.cancerresearchuk.org/cancerstats/types/multiplemyeloma/incidence/index.htm. Cancer Research UK.
2. Kumar SK, Rajkumar SV, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood. 2008 Mar 1;111(5):2516-20.
3. Brenner H, Gondos A, Pulte D. Expected long-term survival of patients diagnosed with multiple myeloma in 2006-2010. Haematologica. 2009 Feb;94(2):270-5.
4. Landgren O, Kyle RA, Pfeiffer RM, Katzmann JA, Caporaso NE, Hayes RB, et al. Monoclonal gammopathy of undetermined significance (MGUS) consistently precedes multiple myeloma: a prospective study. Blood. 2009 May 28;113(22):5412-7.
5. Knudsen LM, Hippe E, Hjorth M, Holmberg E, Westin J. Renal function in newly diagnosed multiple myeloma--a demographic study of 1353 patients. The Nordic Myeloma Study Group. Eur J Haematol. 1994 Oct;53(4):207-12.
6. Eleutherakis-Papaiakovou V, Bamias A, Gika D, Simeonidis A, Pouli A, Anagnostopoulos A, et al. Renal failure in multiple myeloma: incidence, correlations, and prognostic significance. Leuk Lymphoma. 2007 Feb;48(2):337-41.
7. Clark AD, Shetty A, Soutar R. Renal failure and multiple myeloma: pathogenesis and treatment of renal failure and management of underlying myeloma. Blood Rev. 1999 Jun;13(2):79-90.
8. Drayson M, Begum G, Basu S, Makkuni S, Dunn J, Barth N, et al. Effects of paraprotein heavy and light chain types and free light chain load on survival in myeloma: an analysis of patients receiving conventional-dose chemotherapy in Medical Research Council UK multiple myeloma trials. Blood. 2006 Sep 15;108(6):2013-9.
9. Morgan GJ, Davies FE, Gregory WM, Bell SE, Szubert AJ, Navarro Coy N, et al. Cyclophosphamide, thalidomide, and dexamethasone as induction therapy for newly diagnosed multiple myeloma patients destined for autologous stem-cell transplantation: MRC Myeloma IX randomized trial results. Haematologica. 2011 Nov 4.
10. Augustson BM, Begum G, Dunn JA, Barth NJ, Davies F, Morgan G, et al. Early mortality after diagnosis of multiple myeloma: analysis of patients entered onto the United kingdom Medical Research Council trials between 1980 and 2002--Medical Research Council Adult Leukaemia Working Party. J Clin Oncol. 2005 Dec 20;23(36):9219-26.
11. Torra R, Blade J, Cases A, Lopez-Pedret J, Montserrat E, Rozman C, et al. Patients with multiple myeloma requiring long-term dialysis: presenting features, response to therapy, and outcome in a series of 20 cases. Br J Haematol. 1995 Dec;91(4):854-9.
12. Kastritis E, Anagnostopoulos A, Roussou M, Gika D, Matsouka C, Barmparousi D, et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. Haematologica. 2007 Apr;92(4):546-9.
13. Knudsen LM, Hjorth M, Hippe E. Renal failure in multiple myeloma: reversibility and impact on the prognosis. Nordic Myeloma Study Group. Eur J Haematol. 2000 Sep;65(3):175-81.
14. Alexanian R, Barlogie B, Dixon D. Renal failure in multiple myeloma. Pathogenesis and prognostic implications. Arch Intern Med. 1990 Aug;150(8):1693-5.
15. MT Drayson JB, DR Cohen, N Iggo4, WM Gregory SB, A Howie, D Samson,, GH Jackson GG. Serum FLC Levels Can Be Reduced Rapidly; Lower Levels Are Associated with Renal Recovery. IMW 2009: Clinical Lymphoma & Myeloma, Vol. 9, Suppl. 2, S3-S95, 2009; DOI: 10.3816/CLM.2009.s.009, 2009.
16. Gandhi V. Metabolism and mechanisms of action of bendamustine: rationales for combination therapies. Semin Oncol. 2002 Aug;29(4 Suppl 13):4-11.
17. Preiss RTJ, Po¨nisch, W., Niederwieser, D., Matthias, M. & Merkle, K.H. Bendamustine in patients with renal insufficiency. Onkologie. 2003;26(Suppl 5):S131: P717.
18. Gaul L, Mandl-Weber S, Baumann P, Emmerich B, Schmidmaier R. Bendamustine induces G2 cell cycle arrest and apoptosis in myeloma cells: the role of ATM-Chk2-Cdc25A and ATM-p53-p21-pathways. J Cancer Res Clin Oncol. 2008 Feb;134(2):245-53.
19. Ponisch W, Mitrou PS, Merkle K, Herold M, Assmann M, Wilhelm G, et al. Treatment of bendamustine and prednisone in patients with newly diagnosed multiple myeloma results in superior complete response rate, prolonged time to treatment failure and improved quality of life compared to

treatment with melphalan and prednisone--a randomized phase III study of the East German Study Group of Hematology and Oncology (OSHO). J Cancer Res Clin Oncol. 2006 Apr;132(4):205-12.
20. Knop S, Straka C, Haen M, Schwedes R, Hebart H, Einsele H. The efficacy and toxicity of bendamustine in recurrent multiple myeloma after high-dose chemotherapy. Haematologica. 2005 Sep;90(9):1287-8.
21. Haubitz M, Bohnenstengel F, Brunkhorst R, Schwab M, Hofmann U, Busse D. Cyclophosphamide pharmacokinetics and dose requirements in patients with renal insufficiency. Kidney Int. 2002 Apr;61(4):1495-501.
22. Eriksson T, Hoglund P, Turesson I, Waage A, Don BR, Vu J, et al. Pharmacokinetics of thalidomide in patients with impaired renal function and while on and off dialysis. J Pharm Pharmacol. 2003 Dec;55(12):1701-6.
23. Tosi P, Zamagni E, Cellini C, Cangini D, Tacchetti P, Tura S, et al. Thalidomide alone or in combination with dexamethasone in patients with advanced, relapsed or refractory multiple myeloma and renal failure. Eur J Haematol. 2004 Aug;73(2):98-103.
24. Morgan GJ, Davies FE, Gregory WM, Russell NH, Bell SE, Szubert AJ, et al. Cyclophosphamide, thalidomide, and dexamethasone (CTD) as initial therapy for patients with multiple myeloma unsuitable for autologous transplantation. Blood. 2011 Aug 4;118(5):1231-8.
25. Ramasamy K, Hazel B, Mahmood S, Corderoy S, Schey S. Bendamustine in combination with thalidomide and dexamethasone is an effective therapy for myeloma patients with end stage renal disease. Br J Haematol. 2011 Dec;155(5):632-4.
26. Jagannath S, Barlogie B, Berenson JR, Singhal S, Alexanian R, Srkalovic G, et al. Bortezomib in recurrent and/or refractory multiple myeloma. Initial clinical experience in patients with impared renal function. Cancer. 2005 Mar 15;103(6):1195-200.
27. Chanan-Khan AA, Kaufman JL, Mehta J, Richardson PG, Miller KC, Lonial S, et al. Activity and safety of bortezomib in multiple myeloma patients with advanced renal failure: a multicenter retrospective study. Blood. 2007 Mar 15;109(6):2604-6.
28. San Miguel JF, Schlag R, Khuageva NK, Dimopoulos MA, Shpilberg O, Kropff M, et al. Bortezomib plus melphalan and prednisone for initial treatment of multiple myeloma. N Engl J Med. 2008 Aug 28;359(9):906-17.
29. Wolfram Pönisch MA, Ina Wagner, Doreen Hammerschmidt, Ute Kreibich, Andreas Schwarzer, Thomas Zehrfeld, Maik Schwarz, Cornelia Winkelmann, Sirak Petros, Anette Bachmann, Tom Lindner and Dietger Niederwieser. Successful Treatment with Bortezomib in Combination with Bendamustine and Prednisone of Patients with Newly Diagnosed/Untreated Multiple Myeloma and Light Chain Induced Renal Failure. Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract 2938. 2011.
30. James R. Berenson OY, Alberto Bessudo, Ralph V. Boccia, Stephen J. Noga, Donald S. Gravenor, Dipti Patel-Donnelly, Robert S. Siegel, Tarun Kewalramani, Edward J. Gorak, Regina A. Swift and Debra Mayo. Bendamustine Combined with Bortezomib Has Efficacy in Patients with Relapsed or Refractory Multiple Myeloma: A Phase 1/2 Study. Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract 1857. 2011.
31. Jesus G. Berdeja DRC, Patrick Murphy, Ralph V. Boccia, Victor Priego, John D. Hainsworth, Inés M. Macias-Pérez, and Ian W. Flinn. A Phase II Trial of Combined Bendamustine, Bortezomib and Dexamethasone in Newly Diagnosed Multiple Myeloma (MM) Patients Who Are Not Candidates for High-Dose Chemotherapy: Results of a Planned Interim Safety Analysis. Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract 653. 2011.
32. Heinz Ludwig HK, Werner Linkesch, Josef Thaler Richard Greil, Clemens Leitgeb Daniel Heintel, Elisabeth Rauch, Niklas Zojer, Ludek Pour, Adelheid Seebacher and Zdenek Adam. Bortezomib-Bendamustine-Dexamethasone in Patients with relapsed/refractory Multiple Myeloma (MM) Shows Marked Efficacy and Is Well Tolerated, but Assessment of PNP Symptoms Shows Significant Discrepancies between Patients and Physicians. Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract 2928. 2011.
33. Fenk R, Michael M, Zohren F, Graef T, Czibere A, Bruns I, et al. Escalation therapy with bortezomib, dexamethasone and bendamustine for patients with relapsed or refractory multiple myeloma. Leuk Lymphoma. 2007 Dec;48(12):2345-51.

34. Meletios A Dimopoulos MR, Maria Gkotzamanidou, Erasmia Psimenou, Despoina Mparmparoussi, Charis Matsouka, Evangelos Terpos and Efstathios Kastritis. The Role of Novel Agents on Reversibility of Renal Impairment in Newly Diagnosed Patients with Multiple Myeloma; a Single Center Experience on 112 Patients. Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract 3961. 2011.

35. Colin A Hutchison AB, Graham Mead and Mark Cook. An International Study of High Cut-off Haemodialysis for the Management of Myeloma Kidney. Blood (ASH Annual Meeting Abstracts) 2011 118: Abstract 3974. 2011.

36. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. Leukemia. 2006 Sep;20(9):1467-73.

37. Dimopoulos MA, Terpos E, Chanan-Khan A, Leung N, Ludwig H, Jagannath S, et al. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. J Clin Oncol. 2010 Nov 20;28(33):4976-84. Epub 2010 Oct 18.

38. The EuroQol Group (1990). EuroQol-a new facility for the measurement of health-related quality of life. Health Policy 16(3):199-208

39. Fischbach F, Dunning M. Manual of Laboratory and Dianostic Tests, 2004.

40. Bladé J, Samson D, Reece D, Apperley J, Björkstrand B, et al. (1998) Criteria for evaluating disease response and progression in patients with multiple myeloma treated by high-dose therapy and haemopoietic stem cell transplantation. Myeloma Subcommittee of the EBMT. European Group for Blood and Marrow Transplant. British Journal of Haematology, 102, 1115-1123.

41. BGM Durie1, J-L Harousseau2, JS Miguel, J Blade, B Barlogie, et al. International uniform response criteria for multiple myeloma Leukemia 2006, May: 20(10):1–7.

42. Rajkumar SV. Multiple myeloma: 2011 update on diagnosis, risk-stratification and manaement American Journal of Hematology 2011 Jan 86:1, 57-65.

20. APPENDICES

Appendix A: Schedule of Events for Participant Study Visits

Procedures/ Assessments	Screening		Cycles 1 - 4			Cycle 5 & 6 (if applicable)			1 month Follow-up	12 month follow-up
	≤ 21 days before randomisation	≤ 14 days before 1st treatment	Wk 1	Wk 2	Wk 3	Wk 1	Wk 2	Wk 3		
Inclusion / Exclusion criteria	X									
Informed Consent	X									
Complete Medical History	X									
Physical Examination	X		X			X			X	X
Concomitant Medication [1]	X		X	X	X	X	X	X		
Adverse Events [2]	X		X	X	X	X	X	X	X	X
Height	X									
Weight	X		X			X			X	
ECOG performance status score	X		X			X			X	X
Skeletal survey (including spine)	X									
Chest X ray	X									
MRI (if clinically indicated)	X									
ECG	X									
Haematology (FBC) (local) [3]		X	X			X			X	
Biochemistry (local) [4, 5]		X	X			X			X	X[5]
Immunology (local) [6]		X	X			X			X	
Pregnancy test (urine) [7]		X	X			X			X	
Bone Marrow Assessment (local)		X							X	
Central Lab (Birmingham) samples - Blood serum and urine [8]		X	X[8]	X[8]	X[8]				X	
Central Lab (Birmingham) samples - Bone marrow aspirate [9]		X							X	
Central Lab (Oxford) samples- Bone marrow aspirate and slides [10]		X							X	
Drug dispensing & Participant Treatment Diary Card(s) Dexamethasone (Arm A and Arm B) Thalidomide (Arm B only)			X			X				
Accountability & Collection of Participant Treatment Diary Card(s) Dexamethasone (Arm A and Arm B) Thalidomide (Arm B only)					X			X	X	
Administration of Bortezomib Days 1, 4 ,8 &11 of each cycle–**Arm A only** [11]			X	X		X	X			
Administration of Bendamustine Days 1 & 8 of each cycle			X	X		X	X			
QoL questionnaire (EQ-5D-3L)			X			X			X	X
Summary of Treatment(s) received					X			X	X	X
Treatment efficacy information [12]									X	
Survival information								X	X	X

1. Concomitant Medications to be recorded at screening and at start and end of each treatment cycle (see sections 7.3, 7.5)
2. Adverse Events to be recorded during treatment cycles and at 1 and 12 month follow up (see sections 7.3, 7.5)
3. **Haematology**: Haemoglobin, Haematocrit, WBCs, Platelet Count, bilirubin, Neutrophils, Lymphocytes, Monocytes (see section 8.1)
4. Biochemistry: Sodium, Potassium, Total Protein, Albumin, Adjusted Calcium, Bicarbonate, Magnesium, Phosphate, Urea, Creatinine, LFTs, CRP, LDH, Uric acid, Glucose, Creatinine Clearance: in ml/min measured based on the abbreviated MDRD equation : $186 \times (\text{Creat} / 88.4)^{-1.154} \times (\text{Age})^{-0.203}$ x (0.742 if female) x (1.210 if black) using creatinine micromol/L. The calculator for this can be found at http://www.renal.org/egfrcalc/
5. **Biochemistry:** Creatinine, eGFR only at 12 month follow up
6. Immunology: Beta-2 microglobulin, sFLC, Paraprotein, Quantitative Immunoglobulins (see section 8.1)

7. Pregnancy test: For women of child-bearing potential (WCP) Pregnancy test to be performed at screening (not more than 14 days before start of treatment) and again on the day of, or the day before, day 1 of each cycle. Final test should be done approximately 30 days after the last dose of study drug (see section 8.1)

8. Central Lab (Birmingham): Blood 5 ml (EDTA), Blood 10 ml (clotted), Urine sample 20 ml (universal container)(if participant undergoing 24 hour urine collection as an inpatient take 20 ml aliquot). Collect at end of weeks 1, 2, 3, 4, 5, 6, 9 & 12 NB. For cycles 3-4, week 3 sampling only (see protocol section 8.2 & Central Lab Sample Manual).

9. **Central Lab (Birmingham)** Bone marrow aspirate 2 ml (EDTA) (See section 8.2) & Central Lab Sample Manual)

10. Central Lab (Oxford): Bone marrow aspirate: 5ml (EDTA) & 2 unstained slides. For consenting participants only (see section 8.2 & Central Lab Sample Manual)

11. Bortezomib: For cycles 3-4 (and 5-6, where relevant), bortezomib may be given as 1.3 mg/m2 weekly for 3 weeks in a 21 day cycle in combination with Bendamustine and dexamethasone as per local practice. The dosing regimen used must be documented in the CRF.

12. Definition of response to treatment: serum paraprotein, serum & urine FLCs, immunofixation & imaging (if clinically required)

Appendix B: ECOG Performance Status

Grade Description

0 = Normal activity: asymptomatic

1 = Symptomatic: fully ambulatory

2 = Symptomatic: in bed < 50% of time

3 = Symptomatic: in bed > 50% of time - not bedridden

4 = 100% bedridden

Appendix C: International Staging System (ISS)

Stage	Criteria
I	Serum β2 microglobulin <3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Neither stage l or II
III	Serum β2 microglobulin >5.5 mg/L

Appendix D: International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma 1 (36, 27)

Response sub-category	Response Criteria
sCR (Stringent Complete Response)	CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow [2] by immunohistochemistry or immunofluorescence [3]
CR (Complete Response)	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow [2]
VGPR (Very Good Partial Response)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h
PR (Partial Response)	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h If the serum and urine M-protein are not measurable [4], a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
SD (Stable Disease)	Not meeting criteria for CR, VGPR, PR, or progressive disease [5]
Progressive Disease [4]	Increase of ≥ 25% from lowest response value in any one or more of the following: - Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL) [6] - Urine M-component and/or (the absolute increase must be ≥200 mg/24 h) - Only in participants without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL - Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10% [6] - Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas - Development of hypercalcaemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ

	dysfunction (CRAB features [6]. It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] 4. Decrease in haemoglobin of ≥ 2 g/dL [1.25 mmol/L] 5. Rise in serum creatinine by 2 mg/dL or more [177 mol/L or more]
Relapse from CR [4] (to be used only if the end point studied is DFS) [8]	Any one or more of the following: - Reappearance of serum or urine M-protein by immunofixation or electrophoresis - Development of ≥ 5% plasma cells in the bone marrow [7] - Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcaemia)

Note: A clarification to IMWG criteria for coding CR and VGPR in participants in whom the only measurable disease is by serum FLC levels: CR in such participants is defined as a normal FLC ratio of 0.26–1.65 in addition to CR criteria listed above. VGPR in such participants is defined as a >90% decrease in the difference between involved and uninvolved free light chain (FLC) levels.

[1] adapted from BGM Durie et al. International uniform response criteria for multiple myeloma. Leukemia (2006) 1-7.

[2] Confirmation with repeat bone marrow biopsy not needed.

[3] Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of > 4:1 or < 1:2.

[4] All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR participants must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression free survival.

[5] not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates

[6] For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

[7] Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

[8] For purposes of calculating time to progression and progression-free survival, CR participants should also be evaluated using criteria listed above for progressive disease.

Appendix E: Health Questionnaire

Health Questionnaire

English version for the UK

(validated for Ireland)

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

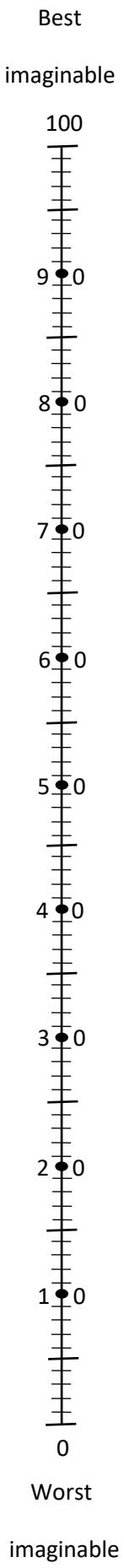
I am moderately anxious or depressed ❑

I am extremely anxious or depressed ❑

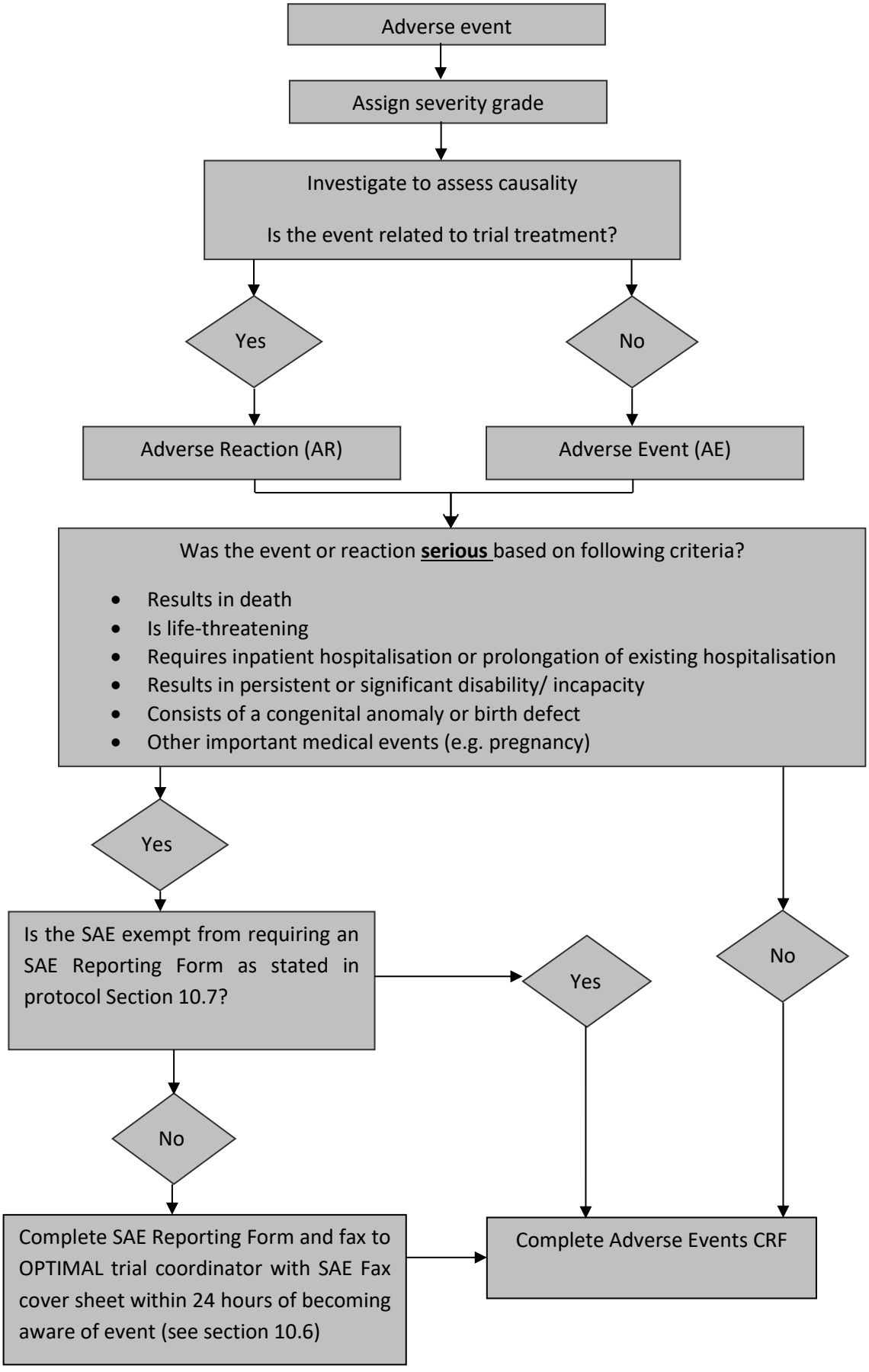
To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state



Appendix F: SAE Reporting Flow Chart



Appendix G: Definition of Women of Childbearing Potential

Women not of childbearing potential include women who
– Are age ≥ 50 years and naturally amenorrhoeic for ≥ 1 year not induced by chemotherapy
– Or have
• Premature ovarian failure confirmed by a specialist gynaecologist
• Previous bilateral salpingo-oophorectomy, or hysterectomy
• XY genotype, Turner's syndrome, uterine agenesis
• Women of childbearing potential are all other women who are menstruating or perimenopausal, even those who abstain from sexual intercourse.

Appendix H: Pregnancy Report Form A

OPTIMAL **OPTIMAL CRF 15a - Pregnancy Form** Page 1 of 4

Participant Study ID ☐☐☐-☐☐☐ Patient Initials ☐☐☐ Date of Birth D D M O N Y Y Y Y

OPTIMAL: A study of Thalidomide, Bendamustine, and Dexamethasone (BTD) vs Bortezomib, Bendamustine, and Dexamethasone (BBD) in patients with renal failure defined as a GFR below 30 mls/ min. Eudract: 2012-003947-31)

Product Exposure During Pregnancy Collection Form A

15.1 EXPOSURE TO STUDY DRUG(S)			
Exposure: Maternal: ☐ Paternal: ☐			
Participant Study ID No.			
Study medication/products(s): ☐ Bendamustine; ☐ Bortezomib; ☐ Thalidomide; ☐ Dexamethasone			
Date of Birth: D D M O N Y Y Y Y			
15.2 MATERNAL INFORMATION			
Initials:			
Date of birth D D M O N Y Y Y Y			Age at time of exposure:
Height (cm):	Weight (kg):		
Ethnic origin:	Occupation:		
Were there any relevant maternal risk factors in the home/work environment (such as chemical exposure, x-rays, history of miscarriages, etc.)?	No ☐	Yes ☐	If yes, please give details:

For Office use only Date form received: D D M O N Y Y Y Y	Date form entered: D D M O N Y Y Y Y	Initials:

Optimal Pregnancy Form CRF version 2 06.11.2014 Sponsor: Oxford University Hospitals NHS Trust

15.3 CURRENT PREGNANCY

1. Date of mother's last menstrual period: D D M O N Y Y Y Y

2. Date pregnancy confirmed: D D M O N Y Y Y Y ☐ Beta Hcg ☐ Urine Test

3. Date of mother's first prenatal exam: D D M O N Y Y Y Y

4. Expected date of delivery: D D M O N Y Y Y Y

5. Is the mother experiencing any medical disorder/problems during this pregnancy? ☐ No ☐ Yes If yes, please give details:

6. Is the mother continuing with the study drugs? ☐ No ☐ Yes ☐ N/A ☐ Unknown

Please specify:

a. Were product(s) taken correctly at the time of gestation? ☐ No ☐ Yes
If no, please explain:

7. List all medications mother used since date of last menstrual period (include study drugs and concomitant drugs, prescription, over-the-counter, vitamins, and herbal preparations)

Medication	Route	Formulation	Dosing regimen			Start date dd/mm/yyyy	End Date dd/mm/yyyy/ Or Ongoing	Exposure time in gestational weeks	Indication
			Amount	Unit	Freq.				
IMPs									
Bortezomib									Trial Medication
Thalidomide									
Other Medications:									
Dexamethasone:									Trial Medication
Bendamustine									Trial Medication

8. Was an ultrasound performed?
☐ No ☐ Yes

If yes, provide date (DD/MON/YYYY) and results of each ultrasound:

For Office use only
Date form received: D D M O N Y Y Y Y
Date form entered: D D M O N Y Y Y Y
Initials:

9. Were any other investigations/diagnostics performed, such as amniocentesis, blood test, urine test, etc? ☐ No ☐ Yes	If yes, provide date (DD/MON/YYYY), test performed andresults of each test performed: D D M O N Y Y Y Y

10. What is the clinical condition of the foetus(es)?	Unknown ☐	Normal ☐	Abnormal ☐	If abnormal, please give details:

11. What is the status of the current pregnancy?

☐ Continuing

☐ Spontaneous abortion Date of abortion: D D M O N Y Y Y Y

☐ Elective abortion Date of procedure: D D M O N Y Y Y Y

15.4 MATERNAL HISTORY

Describe pertinent medical/obstetrical history (include but not limited to endocrine disorders, medical disorders or recent infections requiring treatment, infertility or use of fertility methods):

1. **Substance History**	**No**	**Yes**	**Select all that apply**
Alcohol	☐	☐	Units of alcohol per day:
Tobacco	☐	☐	Cigarettes per day:
Recreational drugs:	☐	☐	Type of drug and frequency:

2. Is there any family history of congenital anomalies, significant obstetrical outcomes or hereditary disorders?	No ☐	Yes ☐	If yes, describe:

15.5 PREVIOUS PREGNANCIES

1. Has mother been pregnant before? No ☐ Yes ☐	Gravida (include present pregnancy)	Para	Abortions: Induced: Spontaneous: Gestational age: _____weeks _____days
	No. of normal outcomes:	No. of abnormal outcomes:	No. of unknown outcomes:

For Office use only Date form received: D D M O N Y Y Y Y	Date form entered: D D M O N Y Y Y Y	Initials:

2. Describe any abnormal outcomes (include spontaneous abortion, ectopics, congenital anomalies, hereditary disorders, stillbirths or intrauterine death, etc):
3. In case of a previous abnormal pregnancy outcome, list all known medications used during the pregnancy:

15.6 PATERNAL HISTORY

Substance History	No	Yes	Select all that apply:
Alcohol	☐	☐	Drinks per day:
Tobacco	☐	☐	Cigarettes per day:
Recreational drugs:	☐	☐	Type of drug and frequency:

15.7 PRINCIPAL INVESTIGATOR DETAILS

Name:

Address:

Phone number:

Email:

Fax Number:

Completed by:

(Print name) _____

Signature: _____ **Date completed:**

Please note: CRFs should only be completed by appropriately qualified personnel detailed on the trial delegation log

For Office use only Date form received: D D M O N Y Y Y Y	Date form entered: D D M O N Y Y Y Y	Initials:

Appendix I: Pregnancy Report Form B

OPTIMAL **OPTIMAL CRF 15b - Pregnancy Form** Page 1 of 4

Participant Study ID ☐☐☐-☐☐☐ Patient Initials ☐☐☐ Date of Birth D D M O N Y Y Y Y

OPTIMAL (A study of Thalidomide, Bendamustine, and Dexamethasone (BTD) vs Bortezomib, Bendamustine, and Dexamethasone (BBD) in patients with renal failure defined as a GFR below 30 mls/ min. Eudract: 2012-003947-31)

Product Exposure During Pregnancy Collection Form B

15.1 EXPOSURE TO STUDY DRUG(S)

Exposure: Maternal: ☐ Paternal: ☐

Participant Study ID No.

Study medication/products(s): ☐ Bendamustine; ☐ Bortezomib; ☐ Thalidomide; ☐ Dexamethasone

Date of Birth: D D M O N Y Y Y Y

15.2 MATERNAL INFORMATION

Initials:

Date of birth D D M O N Y Y Y Y | Age at time of exposure:

(Please complete even if information was already provided in Form A)

15.3 COURSE AND OUTCOME OF PREGNANCY

1. Did the mother experience any medical problems during the course of this pregnancy? ☐ No ☐ Yes — If yes, please give details:

2. List all medications mother used since date of last menstrual period (include study drugs and concomitant drugs, prescription, over-the-counter, vitamins, and herbal preparations, but exclude medication used during labour and delivery)

Medication	Route	Formulation	Dosing regimen			Start date dd/mm/yyyy	End Date dd/mm/yyyy/ Or Ongoing	Exposure time in gestational weeks	Indication
			Amount	Unit	Freq.				
IMPs									
Bortezomib									Trial Medication
Thalidomide									
Other Medications:									
Dexamethasone:									Trial Medication

For Office use only
Date form received: D D M O N Y Y Y Y | Date form entered: D D M O N Y Y Y Y | Initials:

Bendamustine									Trial Medication

3. Did the mother receive any medication during labour and delivery (include anaesthesia, analgesia, labour induction meds.)?

Medication	Route	Formulation	Dosing regimen			Start date dd/mm/yyyy	End Date dd/mm/yyyy/ Or Ongoing	Indication
			Amount	Unit	Freq.			
IMPs								
Bortezomib								Trial Medication
Thalidomide								
Other Medications:								
Dexamethasone:								Trial Medication
Bendamustine								Trial Medication

Please specify the outcome of pregnancy and complete the rest of the form as applicable:

a) Interrupted pregnancy

No ☐

Yes ☐

- ☐ Spontaneous Abortion — D D M O N Y Y Y Y
- ☐ Elective Abortion — D D M O N Y Y Y Y
- ☐ Intrauterine Death (≥20 Gestational Wks) — Interruption date D D M O N Y Y Y Y; Gestational age: Weeks Days

Specify suspected cause for intrauterine death or spontaneous abortion (autopsy report if done):

Describe the developmental status of the foetus (include anomalies):

b) Uninterrupted pregnancy: Delivery date: D D M O N Y Y Y Y

For Office use only		
Date form received: D D M O N Y Y Y Y	Date form entered: D D M O N Y Y Y Y	Initials:

	Gestational age: Weeks Days
What was the method of delivery?	☐ Spontaneous ☐ Forceps ☐ Vacuum Extraction ☐ Caesarean Section ☐ Other, Specify:

15.4 CHARACTERISTICS OF THE BABY

1. General appearance:	☐ Mature	☐ Premature	☐ Post-mature
2. Sex: ☐ Male ☐ Female	Weight (kg):	Length (cm):	Head circumference (cm):
Apgar score: 1min:	5min:	10min:	

3. Clinical condition of the baby:

☐ Normal newborn; ☐ Congenital anomaly; ☐ Neonatal problem; ☐ Neonatal death; ☐ Stillbirth.

(go to Q.6) ↵

Describe the probable cause for the abnormal outcome:

Date of death if applicable: D D M O N Y Y Y Y

4. Was any relationship suspected between the abnormal pregnancy outcome and the use of the study drug(s)?

	Causality-Could this have been caused by study drug?	**Expectedness**-If related, was this expected?
Thalidomide	☐ Related; ☐ Unrelated.	☐ Expected; ☐ Unexpected.
Bendamustine	☐ Related; ☐ Unrelated.	☐ Expected; ☐ Unexpected.
Bortezomib	☐ Related; ☐ Unrelated.	☐ Expected; ☐ Unexpected.
Dexamethasone	☐ Related; ☐ Unrelated.	☐ Expected; ☐ Unexpected.

5. Was any relationship suspected between the abnormal pregnancy outcome and the use of **CONCOMITANT** medications? ☐ No ☐ Yes			If yes please give details:
6. Was the baby's hospitalisation prolonged?	**No** ☐	**Yes** ☐	If yes please give details:
7. Did the baby receive any medical therapy different from normal newborn care?	☐	☐	If yes please give details:
8. Is the baby being breastfed?	☐	☐	

For Office use only Date form received: D D M O N Y Y Y Y	Date form entered: D D M O N Y Y Y Y	Initials:

15.5 PRINCIPAL INVESTIGATOR DETAILS
Name: Address: Phone number: Email: Fax Number:
Person completing report (please note you must be on the delegation log) Name: Signature: Date of Signing: Designation: Contact Telephone: Email:

Completed by:

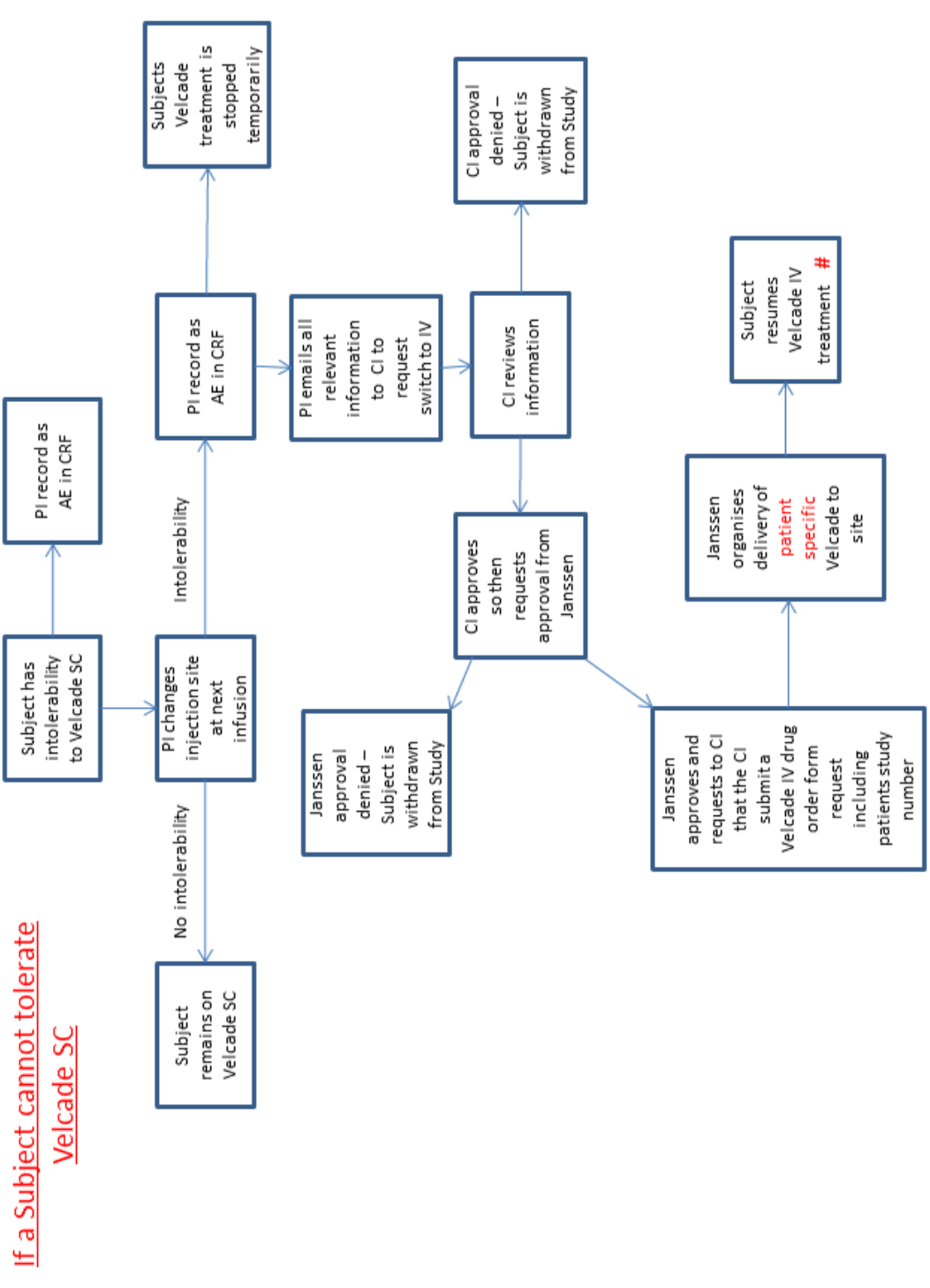
(Print name) _____

Signature: _____ **Date completed:**

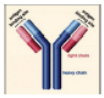
Please note: CRFs should only be completed by appropriately qualified personnel detailed on the trial delegation log

For Office use only			
Date form received: D D M C N Y Y Y Y	Date form entered: D D M C N Y Y Y Y	Initials:

Appendix J: Flowchart for Bortezomib SC to IV switch



Appendix K: OPTIMAL Trial Schema



OPTIMAL

OPTIMAL Trial Schema

Trial Entry

Patient Information Sheet provided to renal failure patient with suspected myeloma

↓

CONSENT

↓

Screening Assessments

- Full medical history of myeloma including date of diagnosis, staging and location(s) of bone disease as per standard of care
- Treatment history including all medications, treatments and therapies used in prior 4 weeks as well as those currently being taken
- Physical examination visit including height, weight, ECOG performance status (protocol Appendix B) and baseline neuropathy
- Skeletal Survey and MRI (if clinically indicated), chest X-ray and ECG
- Adverse events (from date of consent)
- EGFR based on abbreviated MDRD (http://www.renal.org.eGFRcalc/)
- Urine pregnancy test for women of child-bearing potential (for definition see protocol Appendix F)
- Local clinical haematology, immunology, serum chemistry and bone marrow assessment

Central Samples (sent to Birmingham)

- Bone marrow aspirate 2 ml (EDTA)
- Blood 5 ml (EDTA)
- Blood 10 ml (clotted)
- Urine sample 20 ml (universal container)

Central Samples (sent to Oxford)

- Bone marrow 5 ml (EDTA)
- Two unstained slides of bone marrow

↓

CHECK ELIGIBILITY

Inclusion Criteria:

- Participant is willing and able to give informed consent for participation in the trial.
- Male or Female, aged 18 years or above.
- Patients attending NHS Haemato-oncology centres
- Patients with newly diagnosed symptomatic myeloma
- GFR <30mls/min
- Chronic kidney disease (CKD) staging is based on estimated or measured Glomerular filtration rate. CKD stage 4 (15-29ml/min) and CKD stage 5 (<15ml/min) are eligible to enter the study. It is expected centres will consider use of fluid resuscitation and pulsed dose of steroid therapy in this group of patients to salvage renal function prior to trial screening.
- A number of patients with newly diagnosed myeloma and renal failure will have a pre-existing medical condition (hypertension, diabetes etc.) causing renal damage. Where there is a medical condition (e.g.; hypertension, diabetes) which may cause renal damage, there must have been a further decline (≥15 mls/min GFR) between previous steady state and the study screening.
- Female participants of childbearing potential and male patients whose partner is a woman of childbearing potential must be prepared to use contraception in accordance with (and consent to) the Celgene-approved process for thalidomide and lenalidomide Risk Management and Pregnancy Prevention Programme.
- Women of childbearing potential must have a negative pregnancy test performed by a healthcare professional in accordance with the Celgene-approved process for thalidomide and lenalidomide Risk Management and Pregnancy Prevention.
- Free of prior malignancies for ≥ 2 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, localised prostate cancer or carcinoma "in-situ" of the cervix or breast.
- In the Investigator's opinion, is able and willing to comply with all trial requirements.
- Willing to allow his or her General Practitioner and consultant, if appropriate, to be notified of participation in the trial.

Exclusion Criteria:

- Female participant who is pregnant, lactating or planning pregnancy during the course of the trial or the female partner of a male participant planning a pregnancy during the course of the trial
- Aged <18 years
- Known allergy to investigational drugs
- Any other significant disease or disorder which, in the opinion of the Investigator, may either put the participants at risk because of participation in the trial, or may influence the result of the trial, or the participant's ability to participate in the trial
- Any of the following laboratory abnormalities:
  - Absolute neutrophil count (ANC) < 1.0 x10^9/L
  - Platelet count <75 x10^9/L
  - Serum SGOT/AST or SGPT/ALT >3 x upper limit of normal
- Use of any standard/experimental anti myeloma drug therapy excluding dexamethasone 14 days prior to trial entry
- CKD stages < 4
- Intention to use a physical method of serum free light chain removal such as plasma exchange or high cut off dialysis
- Grade 2 neuropathy or more (NCICTCAE v 4.0) will preclude use of thalidomide and bortezomib
- Participants who have participated in another research trial involving an investigational product in the past 12 weeks
- Contraindicated to receive any one of study drugs: thalidomide, bortezomib, bendamustine based on summary of product characteristics.

↓

RANDOMISATION

Arm A:	**Arm B:**
Bortezomib, Bendamustine and Dexamethasone (BBD) (4-6 cycles)	Thalidomide, Bendamustine and Dexamethasone(BTD) (4-6 cycles)

Warwick Clinical Trials Unit
Tel:02476 150 402 (Mon-Fri, 9am to 5pm) Fax: 02476 151 586

OPTIMAL_Trial Schema_V4.0_12Oct2016 Sponsor: Oxford University Hospitals NHS Foundation Trust

OPTIMAL Trial Schema

On –Treatment

TREATMENT: CYCLES 1-4

(see Protocol for dose reductions and supportive therapy)

1. Treatments

Arm A
Days 1,4,8 & 11 bortezomib 1.3 mg/m^2 subcutaneous*
Days 1 & 8 bendamustine 60 mg/m^2 IV
Days 1-2, 4-5, 8-9, & 11-12 dexamethasone 40 mg daily orally
Patients >70 years dose of dexamethasone reduced from 40-

Arm B
Days 1-21 thalidomide 100 mg daily orally
Days 1 & 8 bendamustine 60 mg/m^2 IV
Days 1-2, 4-5, 8-9, & 11-12 dexamethasone 40 mg daily orally
Patients >70 years dose of dexamethasone reduced from 40-

2. Assessments (both arms)

- Physical examination including weight & ECOG
- Concomitant medication
- Dispensing and Accountability (Patient Treatment Diary)
- Local clinical haematology, biochemistry & immunology
- Urine pregnancy test
- Quality of Life questionnaire
- Adverse events
- Survival

3. Central Samples (sent to Birmingham– both arms)
end of weeks 1, 2, 3, 4, 5, 6, 9 & 12:

- Blood 5 ml (EDTA)
- Blood 10 ml (clotted)
- Urine sample 20 ml (universal container)

TREATMENT: CYCLES 5-6

(for participants not suitable for ASCT)

1. Treatments

Arm A
Days 1,4,8 & 11 bortezomib 1.3 mg/m^2 subcutaneous*
Days 1 & 8 bendamustine 60 mg/m^2 IV
Days 1-2, 4-5, 8-9, & 11-12 dexamethasone 40 mg daily orally
Patients >70 years dose of dexamethasone reduced from 40-20 mg daily
*[*IV available if patient intolerant of SC]*

Arm B
Days 1-21 thalidomide 100 mg daily orally
Days 1 & 8 bendamustine 60 mg/m^2 IV
Days 1-2, 4-5, 8-9, & 11-12 dexamethasone 40 mg daily orally
Patients >70 years dose of dexamethasone reduced from 40-20 mg daily

2. Assessments (both arms)

- Physical examination including weight & ECOG
- Concomitant medication
- Dispensing and accountability (Patient Treatment Diary)
- Local clinical haematology, biochemistry & immunology
- Urine pregnancy test
- Quality of Life questionnaire
- Adverse events
- Survival

3. Central Samples (sent to Birmingham– both arms)
end of weeks 1, 2, 3, 4, 5, 6, 9 & 12:

- None

Follow-Up

ONE MONTH FOLLOW-UP

(for all patients approx. 30 days after final treatment or discontinuation of treatment)

1. Assessments (both arms)

- Physical examination including weight & ECOG
- Drug accountability (Patient Treatment Diary)
- Local clinical haematology, biochemistry, immunology, and bone marrow assessment
- Urine pregnancy test
- Quality of Life questionnaire
- Adverse events
- Treatment Efficacy and Survival
- Survival

2. Central Samples (Birmingham– both arms)

- Bone marrow aspirate 2 ml (EDTA)
- Blood 5 ml (EDTA)
- Blood 10 ml (clotted)
- Urine sample 20 ml (universal container)

3. Central Samples (Oxford– both arms)

- Bone marrow EDTA 5 ml (EDTA)
- Two unstained slides of bone marrow

12 MONTH FOLLOW-UP

(for all patients approx. 12 months after randomisation

1. Assessments (both arms)

- Physical examination including ECOG
- Local clinical biochemistry
- Quality of Life questionnaire
- Adverse Events
- Disease status
- Clinical Assessment
- Hospital admission history since end of trial treatment
- Subsequent anti-myeloma treatment
- Survival

2. Central Samples

- None

OPTIMAL Clinical Trial Coordinator: Tel: 01865 223353 Email: optimal.trial@nhs.net

Birmingham Samples to: Clinical Immunology Service, PO Box 1894, Vincent Drive, Edgbaston, Birmingham, B15 2SZ

Oxford Samples to: Molecular Haematology Lab, Level 4, John Radcliffe Hospital, Headley Way, OX3 9DU